

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

This Page Blank (uspto)

09623705
5060
PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

PCT/ SE 00 / 0 1 2 5 2
09/623705

REC'D 24 AUG 2000

WIPO

PCT

**Intyg
Certificate**

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) Sökande AstraZeneca AB, Södertälje SE
Applicant (s)

(21) Patentansökningsnummer 9902269-1
Patent application number

(86) Ingivningsdatum 1999-06-16
Date of filing

Stockholm, 2000-08-14

För Patent- och registreringsverket
For the Patent- and Registration Office

Åsa Dahlberg
Åsa Dahlberg

Avgift
Fee

**PRIORITY
DOCUMENT**
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

**PATENT- OCH
REGISTRERINGSVERKET**
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

PHARMACEUTICALLY ACTIVE COMPOUNDS

Field of the Invention

5 This invention relates to novel pharmaceutically useful compounds, in particular compounds which are useful in the treatment of cardiac arrhythmias.

Background and Prior Art

10

Cardiac arrhythmias may be defined as abnormalities in the rate, regularity, or site of origin of the cardiac impulse or as disturbances in conduction which causes an abnormal sequence of activation. Arrhythmias may be classified clinically by means of the presumed site of origin (i.e. as
15 supraventricular, including atrial and atrioventricular, arrhythmias and ventricular arrhythmias) and/or by means of rate (i.e. bradyarrhythmias (slow) and tachyarrhythmias (fast)).

In the treatment of cardiac arrhythmias, the negative outcome in clinical
20 trials (see, for example, the outcome of the Cardiac Arrhythmia Suppression Trial (CAST) reported in New England Journal of Medicine, 321, 406 (1989)) with "traditional" antiarrhythmic drugs, which act primarily by slowing the conduction velocity (class I antiarrhythmic drugs), has prompted drug development towards compounds which selectively delay cardiac
25 repolarization, thus prolonging the QT interval. Class III antiarrhythmic drugs may be defined as drugs which prolong the trans-membrane action potential duration (which can be caused by a block of outward K^+ currents or from an increase of inward ion currents) and refractoriness, without affecting cardiac conduction.

One of the key disadvantages of hitherto known drugs which act by delaying repolarization (class III or otherwise) is that they all are known to exhibit a unique form of proarrhythmia known as *torsades de pointes* (turning of points), which may, on occasion be fatal. From the point of view of safety, the minimisation of this phenomenon (which has also been shown to be exhibited as a result of administration of non-cardiac drugs such as phenothiazines, tricyclic antidepressants, antihistamines and antibiotics) is a key problem to be solved in the provision of effective antiarrhythmic drugs.

10

Antiarrhythmic drugs based on bispidines (3,7-diazabicyclo[3.3.1]nonanes), are known from *inter alia* international patent application WO 91/07405, European patent applications 306 871, 308 843 and 655 228 and US patents 3,962,449, 4,556,662, 4,550,112, 4,459,301 and 5,468,858, as well as journal articles including *inter alia* J. Med. Chem. **39**, 2559, (1996), Pharmacol. Res., **24**, 149 (1991), Circulation, **90**, 2032 (1994) and Anal. Sci. **9**, 429, (1993). Known bispidine-based antiarrhythmic compounds include bisaramil (3-methyl-7-ethyl-9 α ,4'-(Cl-benzoyloxy)-3,7-diazabicyclo[3.3.1]nonane), tedisamil (3',7'-bis(cyclopropylmethyl)spiro(cyclopentane-1,9'-3,7]diazabicyclo-[3.3.1]nonane), SAZ-VII-22 (3-(4-chlorobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane), SAZ-VII-23 (3-benzoyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane), GLG-V-13 (3-[4-(1H-imidazol-1-yl)benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane), KMC-IV-84 (7-[4'-(1H-imidazolo-1-yl)benzenesulfonyl]-3-isopropyl-3,7-diazabicyclo[3.3.1]nonane dihydro-perchlorate and ambasilide (3-(4-aminobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane).

25

We have surprisingly found that a novel group of bispidine-based compounds exhibit electrophysiological activity, preferably class III

Disclosure of the Invention

5

The diagram shows a chemical structure of a substituted benzene ring. The benzene ring is at the bottom left, with a substituent R^6 at the para position. The ring is connected to a carbon atom labeled B . This carbon atom is also bonded to a group D and a group R^4 . The carbon atom B is further connected to a nitrogen atom labeled A . This nitrogen atom is part of a complex side chain that includes a bridgehead nitrogen atom, a carbonyl group ($C=O$), and a group X bonded to R . The side chain also features several other substituents labeled R^2 , R^3 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , and R^{5f} .

10 **wherein**

R¹ represents C₁₋₁₂ alkyl, -(CH₂)_a-aryl, or -(CH₂)_a-Het¹ (all of which are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, halo, cyano, nitro, C₁₋₄ alkyl and/or C₁₋₄ alkoxy);

a represents 0, 1, 2, 3, or 4;

Het¹ represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

X represents O or S;

R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} and R^{5f} independently represent H or C_{1-3} alkyl;

5

R^2 and R^3 independently represent H, C_{1-4} alkyl (optionally substituted and/or terminated with one or more nitro or cyano groups), OR^7 , $N(R^{7a})R^{7b}$, $OC(O)R^8$ or together form $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$;

10 R^7 and R^8 independently represent H, C_{1-6} alkyl or $-(CH_2)_b$ -aryl (which latter two groups are optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy);

R^{7a} and R^{7b} independently represent H or C_{1-6} alkyl;

15 b represents 0, 1, 2, 3 or 4;

R^4 represents H or C_{1-6} alkyl;

D represents H, C_{1-4} alkyl, $-OR^9$, or $-(CH_2)_cN(R^{10})(R^{11})$;

20 R^9 represents H, C_{1-6} alkyl, $-C(O)R^{12}$, $-(CH_2)_d$ -aryl or $-(CH_2)_d$ -Het² (which latter three groups are optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)R^{13}$, $C(O)OR^{14}$ and/or $-N(H)S(O)_eR^{15}$);

25 R^{10} represents H, C_{1-6} alkyl, $-(CH_2)_f$ -aryl, $-C(NH)NH_2$, $-S(O)_2R^{15a}$, $-[C(O)]_gN(R^{16})(R^{17})$, $-C(O)R^{18}$ or $-C(O)OR^{19}$;

e represents 0, 1 or 2;

g represent 1 or 2;

R^{11} represents H, C_{1-6} alkyl, $-C(O)R^{20}$ or $-(CH_2)_h$ -aryl (which latter group is optionally substituted and/or terminated (as appropriate) by one or more

substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl and/or C₁₋₆ alkoxy);

R¹², R¹³, R¹⁴, R¹⁶, R¹⁷, R¹⁸, R¹⁹ and R²⁰ independently represent H, C₁₋₆ alkyl, Het³ or -(CH₂)_j-aryl (which latter three groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl and/or C₁₋₆ alkoxy);

R¹⁵ and R^{15a} independently represent C₁₋₆ alkyl, aryl or -(CH₂)_k-aryl (all of which are all optionally substituted and/or terminated (as appropriate) by one or more substituents chosen from halo, nitro, C₁₋₆ alkyl and/or C₁₋₆ alkoxy);

c, d, f, h, j and k independently represent 0, 1, 2, 3 or 4;

Het² and Het³ independently represent five to ten-membered heterocyclic rings containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R⁶ represents one or more optional substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl (optionally terminated by N(H)C(O)OR^{20a}), C₁₋₆ alkoxy, -C(O)N(H)R²¹, -NHC(O)N(H)R²², -N(H)S(O)₂R²³ and/or -OS(O)₂R²⁴;

R²¹ and R²² independently represent H or C₁₋₆ alkyl;

R^{20a}, R²³ and R²⁴ independently represent C₁₋₆ alkyl;

A represents a single bond, C₁₋₆ alkylene, -N(R²⁵)(CH₂)_m-, -O(CH₂)_m- or -(CH₂)_mC(H)(OR²⁵)(CH₂)_n- (in which latter three groups, the -(CH₂)_m- group is attached to the bispidine nitrogen atom and which latter four groups are optionally substituted by one or more -OH groups);

B represents a single bond, C_{1-4} alkylene, $-(CH_2)_pN(R^{26})-$, $-(CH_2)_pS(O)_q-$, $-(CH_2)_pO-$ (in which three latter groups, the $-(CH_2)_p-$ group is attached to the carbon atom bearing D and R^4), $-C(O)N(R^{26})-$ (in which latter group, the $-C(O)-$ group is attached to the carbon atom bearing D and R^4),
 5 $-N(R^{26})C(O)O(CH_2)_p-$ or $-N(R^{26})(CH_2)_p-$ (in which latter two groups, the $N(R^{26})$ group is attached to the carbon atom bearing D and R^4);

m, n and p independently represent 0, 1, 2, 3 or 4;

q represents 0, 1 or 2;

R^{25} represents H, C_{1-6} alkyl or $C(O)R^{27}$;

10 R^{26} represents H or C_{1-6} alkyl;

R^{27} represents H, C_{1-6} alkyl, Her^4 or $-(CH_2)_r-aryl$ (which latter two groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

15 Her^4 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

r represents 0, 1, 2, 3 or 4;

20 or a pharmaceutically acceptable derivative thereof;

provided that:

(a) R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} and R^{5f} do not all simultaneously represent H;

(b) R^{5a} and R^{5b} do not represent C_{1-3} alkyl when R^{5c} , R^{5d} , R^{5e} and R^{5f} all
 25 represent H; and

(c) when D represents -OH or $-(CH_2)_cN(R^{10})R^{11}$ in which c represents 0, then:-

(i) A does not represent $-N(R^{25})(CH_2)_m-$, $-O(CH_2)_m-$ or $-(CH_2)_mC(H)(OR^{25})(CH_2)_n-$ (in which n is 0); and/or

(ii) p does not represent 0 when B represents $-(CH_2)_pN(R^{26})-$,
 $-(CH_2)_pS(O)_q-$ or $-(CH_2)_pO-$,

which compounds are referred to hereinafter as "the compounds of the
 5 invention".

Aryl groups that may be mentioned include C_{6-10} aryl groups, such as phenyl, naphthyl and the like. Oxyaryl groups that may be mentioned include C_{6-10} oxyaryl groups, such as oxyphenyl (phenoxy), oxynaphthyl
 10 (naphthoxy) and the like. When substituted, aryl and aryloxy groups are preferably substituted by between one and three substituents.

Het¹, Het², Het³ and Het⁴ groups that may be mentioned include those containing 1 to 4 heteroatoms (selected from the group oxygen, nitrogen
 15 and/or sulfur) and in which the total number of atoms in the ring system is between five and ten. Het (Het¹, Het², Het³ and Het⁴) groups may be wholly/partly aromatic in character and may be bicyclic. Heterocyclic groups that may be mentioned include morpholinyl, thiazolyl, oxazolyl, isoxazolyl, cinnolinyl, quinazolinyl, phthalazinyl, purinyl, benzimidazolyl,
 20 pyrimidinyl, piperazinyl, pyrazinyl, piperidinyl, pyridinyl, pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, triazolyl, imidazolyl, quinolinyl, isoquinolinyl, dioxanyl, benzodioxanyl, benzodioxolyl, benzodioxepanyl, benzomorpholinyl, indolyl, pyrazolyl, pyrrolyl, benzothiophenyl, thiophenyl, chromanyl, thiochromanyl, benzofuranyl, pyranyl,
 25 tetrahydropyranyl, tetrahydrofuranyl, furanyl and the like. Substituents on Het (Het¹, Het², Het³ and Het⁴) groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of Het (Het¹, Het², Het³ and Het⁴) groups may be *via* any atom in the ring system including (where appropriate) a heteroatom. Het (Het¹,

Het², Het³ and Het⁴) groups may optionally be in the N- or S-oxidised form.

Pharmaceutically acceptable derivatives include salts and solvates. Salts which may be mentioned include acid addition salts. Pharmaceutically acceptable derivatives also include C₁₋₄ alkyl quaternary ammonium salts and N-oxides, provided that, when a N-oxide is present:

- (a) no Het (Het¹, Het², Het³, Het⁴) groups contain an unoxidised S-atom;
- (b) X does not represent S;
- (c) q does not represent 0, when B represents $-(CH_2)_pS(O)_q-$; and/or
- (d) e does not represent 0, when R⁹ is substituted by N(H)S(O)_eR¹⁵.

The compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

15

The compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric esters by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

25

- Alkyl groups that $R^1, R^2, R^3, R^4, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R^6, R^7, R^{7a}, R^{7b}, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{15a}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{20a}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}$ and D may represent, and with which $R^1, R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{15a}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$ and R^{27} may be substituted; and alkoxy groups that R^6 may represent, and with which $R^1, R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{15a}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}$ and R^{27} may be substituted, may be linear or, when there is a sufficient number (i.e. three) of carbon atoms, be branched and/or cyclic. Further, when there is a sufficient number (i.e. four) of carbon atoms, such alkyl and alkoxy groups may also be part cyclic/acyclic. Such alkyl and alkoxy groups may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen and/or substituted by one or more fluoro groups.
- Alkylene groups that A and B may represent, and $-(CH_2)-$ containing groups that R^1, R^2 and R^3 (together), $R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{15a}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{27}, A, B$ and D may include, may be linear or, when there is a sufficient number (i.e. two) of carbon atoms, be branched. Such alkylene groups and $-(CH_2)-$ containing chains may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen.

As used herein, the term "halo" includes fluoro, chloro, bromo or iodo.

- Abbreviations are listed at the end of this specification.

Preferred compounds of the invention include those in which:

R^1 represents optionally substituted $-(CH_2)_a$ -phenyl in which a is 0, 1, 2 or 3, or, preferably, optionally substituted, optionally unsaturated, linear,

- branched or cyclic, C_{1-8} alkyl (which latter group may also be interrupted by an oxygen atom);
- R^2 represents H;
- R^3 represents H;
- 5 R^4 represents H or C_{1-3} alkyl;
- R^{5a} and R^{5b} either both represent H or both represent methyl;
- R^{5c} , R^{5d} , R^{5e} and R^{5f} independently represent H or C_{1-2} alkyl;
- R^6 represents one or more substituents selected from C_{1-6} alkyl (which alkyl group is optionally terminated by a $N(H)C(O)OR^{20a}$ group (in which R^{20a} represents C_{1-5} alkyl)), cyano, nitro, amino, $C(O)N(H)R^{21}$ and/or
- 10 $-N(H)S(O)_2R^{23}$;
- X represents O;
- A represents a single bond or linear, or branched, C_{1-4} alkylene (which group is also optionally interrupted by O);
- 15 B represents a single bond, C_{1-4} alkylene, $-(CH_2)_pO-$ or $-(CH_2)_pN(R^{26})-$ (in which latter two cases p is 1, 2 or 3);
- D represents H, OR^9 (in which R^9 represents H, C_{1-3} alkyl or optionally substituted phenyl) or $N(H)R^{10}$ (in which R^{10} represents H or C_{1-4} alkyl);
- when the bispidine nitrogen bearing A optionally bears a C_{1-4} alkyl group,
- 20 thus forming a quaternary ammonium salt, the alkyl group is a methyl group.

More preferred compounds of the invention include those in which:

- R^1 represents linear or branched C_{2-6} alkyl;
- 25 R^4 represents H;
- R^{5a} and R^{5b} both represent H;
- R^6 represents cyano, preferably in the *para* position relative to B;
- A represents C_{1-4} alkylene;
- B represents a single bond or $-(CH_2)_pO-$ (in which p is 1 or 2);

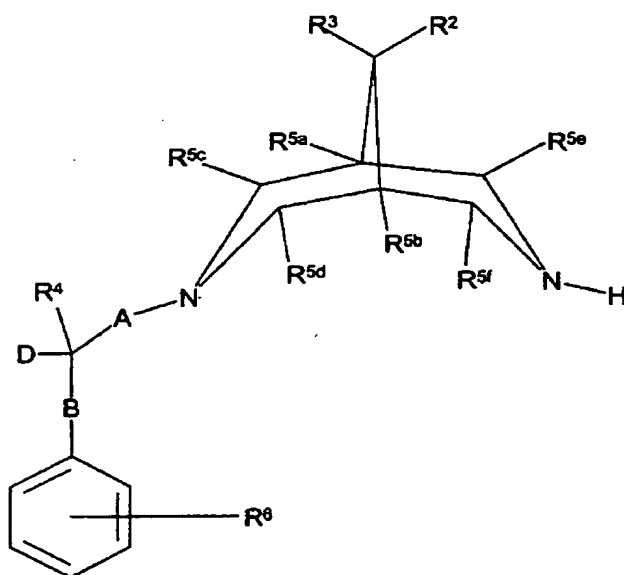
D represents H, OH, NH₂ or phenoxy (optionally substituted on the phenyl ring by one or more C₁₋₃ alkoxy groups).

Preferred compounds of the invention include the compounds of Examples
5 described hereinafter.

Preparation

According to the invention there is also provided a process for the
10 preparation of compounds of formula I which comprises:

(a) reaction of a compound of formula II,



15 wherein R², R³, R⁴, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R⁶, A, B and D are as hereinbefore defined with a compound of formula III,

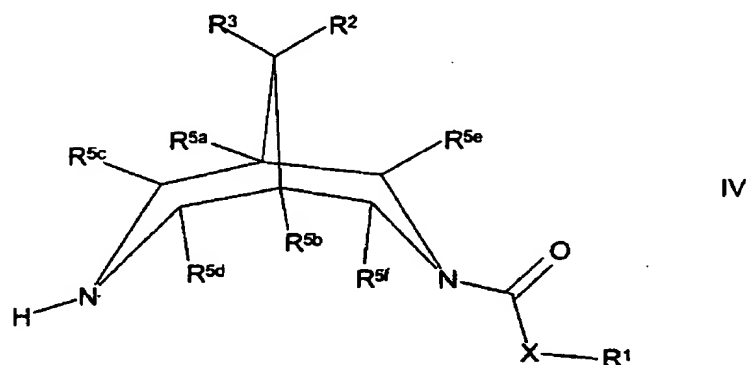


wherein L¹ represents a leaving group, such as Hal, imidazolyl or -OC(O)XR¹, Hal represents Cl, Br or I, and R¹ and X are as hereinbefore

defined, for example at or above room temperature in the presence of a suitable base (e.g. aqueous NaOH, K_2CO_3 or triethylamine) and an appropriate organic solvent (e.g. CH_2Cl_2 , THF, acetonitrile, toluene, or mixtures of such solvents);

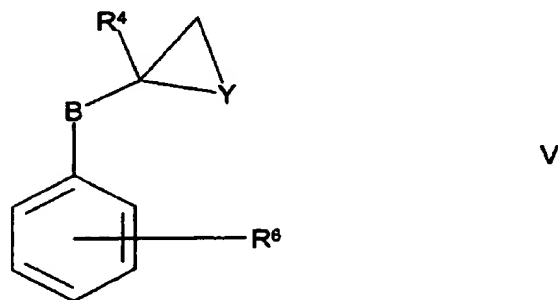
5

(b) for compounds of formula I in which A represents CH_2 and D represents $-OH$ or $-N(H)R^{10}$, wherein R^{10} is as hereinbefore defined, reaction of a compound of formula IV,



10

wherein R^1 , R^2 , R^3 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} and X are as hereinbefore defined, with a compound of formula V,



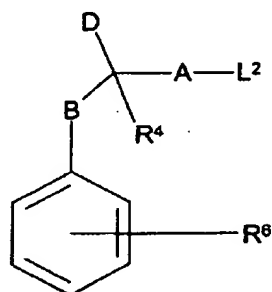
15

wherein Y represents O or $N(R^{10})$ and R^4 , R^6 , R^{10} and B are as hereinbefore defined, for example at elevated temperature (e.g. $60^\circ C$ to reflux) in the

13

presence of a suitable solvent (e.g. a lower alkyl alcohol (e.g. IPA), acetonitrile, or a mixture of a lower alkyl alcohol and water);

- (c) reaction of a compound of formula IV, as hereinbefore defined, with a
5 compound of formula VI,



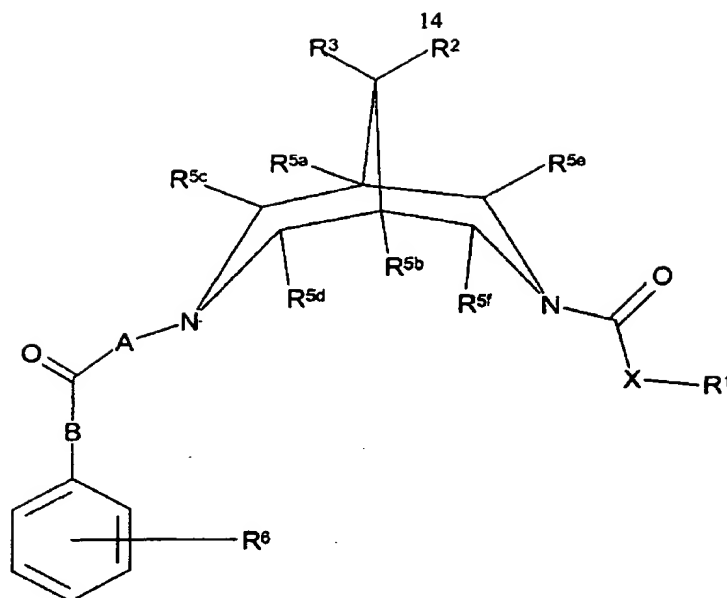
VI

- wherein L^2 represents a leaving group (e.g. mesylate, tosylate or Hal, where Hal is as hereinbefore defined) and R^4 , R^6 , A, B and D are as
10 hereinbefore defined, for example at elevated temperature (e.g. between 35°C and reflux temperature) in the presence of a suitable base (e.g. triethylamine or K_2CO_3) and an appropriate organic solvent (e.g. acetonitrile or dimethylsulfoxide);

15

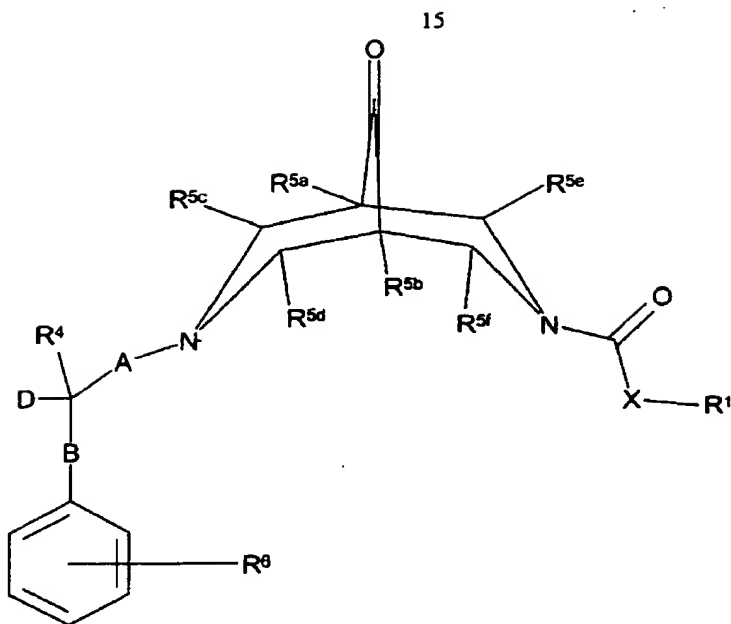
- (d) for compounds of formula I in which D represents H or OH and R^4 represents H, reduction of a compound of formula VII,

16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000
1001
1002
1003
1004
1005
1006
1007
1008
1009
1010
1011
1012
1013
1014
1015
1016
1017
1018
1019
1020
1021
1022
1023
1024
1025
1026
1027
1028
1029
1030
1031
1032
1033
1034
1035
1036
1037
1038
1039
1040
1041
1042
1043
1044
1045
1046
1047
1048
1049
1050
1051
1052
1053
1054
1055
1056
1057
1058
1059
1060
1061
1062
1063
1064
1065
1066
1067
1068
1069
1070
1071
1072
1073
1074
1075
1076
1077
1078
1079
1080
1081
1082
1083
1084
1085
1086
1087
1088
1089
1090
1091
1092
1093
1094
1095
1096
1097
1098
1099
1100
1101
1102
1103
1104
1105
1106
1107
1108
1109
1110
1111
1112
1113
1114
1115
1116
1117
1118
1119
1120
1121
1122
1123
1124
1125
1126
1127
1128
1129
1130
1131
1132
1133
1134
1135
1136
1137
1138
1139
1140
1141
1142
1143
1144
1145
1146
1147
1148
1149
1150
1151
1152
1153
1154
1155
1156
1157
1158
1159
1160
1161
1162
1163
1164
1165
1166
1167
1168
1169
1170
1171
1172
1173
1174
1175
1176
1177
1178
1179
1180
1181
1182
1183
1184
1185
1186
1187
1188
1189
1190
1191
1192
1193
1194
1195
1196
1197
1198
1199
1200
1201
1202
1203
1204
1205
1206
1207
1208
1209
1210
1211
1212
1213
1214
1215
1216
1217
1218
1219
1220
1221
1222
1223
1224
1225
1226
1227
1228
1229
1230
1231
1232
1233
1234
1235
1236
1237
1238
1239
1240
1241
1242
1243
1244
1245
1246
1247
1248
1249
1250
1251
1252
1253
1254
1255
1256
1257
1258
1259
1260
1261
1262
1263
1264
1265
1266
1267
1268
1269
1270
1271
1272
1273
1274
1275
1276
1277
1278
1279
1280
1281
1282
1283
1284
1285
1286
1287
1288
1289
1290
1291
1292
1293
1294
1295
1296
1297
1298
1299
1300
1301
1302
1303
1304
1305
1306
1307
1308
1309
1310
1311
1312
1313
1314
1315
1316
1317
1318
1319
1320
1321
1322
1323
1324
1325
1326
1327
1328
1329
1330
1331
1332
1333
1334
1335
1336
1337
1338
1339
1340
1341
1342
1343
1344
1345
1346
1347
1348
1349
1350
1351
1352
1353
1354
1355
1356
1357
1358
1359
1360
1361
1362
1363
1364
1365
1366
1367
1368
1369
1370
1371
1372
1373
1374
1375
1376
1377
1378
1379
1380
1381
1382
1383
1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414
1415
1416
1417
1418
1419
1420
1421
1422
1423
1424
1425
1426
1427
1428
1429
1430
1431
1432
1433
1434
1435
1436
1437
1438
1439
1440
1441
1442
1443
1444
1445
1446
1447
1448
1449
1450
1451
1452
1453
1454
1455
1456
1457
1458
1459
1460
1461
1462
1463
1464
1465
1466
1467
1468
1469
1470
1471
1472
1473
1474
1475
1476
1477
1478
1479
1480
1481
1482
1483
1484
1485
1486
1487
1488
1489
1490
1491
1492
1493
1494
1495
1496
1497
1498
1499
1500
1501
1502
1503
1504
1505
1506
1507
1508
1509
1510
1511
1512
1513
1514
1515
1516
1517
1518
1519
1520
1521
1522
1523
1524
1525
1526
1527
1528
1529
1530
1531
1532
1533
1534
1535
1536
1537
1538
1539
1540
1541
1542
1543
1544
1545
1546
1547
1548
1549
1550
1551
1552
1553
1554
1555
1556
1557
1558
1559
1560
1561
1562
1563
1564
1565
1566
1567
1568
1569
1570
1571
1572
1573
1574
1575
1576
1577
1578
1579
1580
1581
1582
1583
1584
1585
1586
1587
1588
1589
1590
1591
1592
1593
1594
1595
1596
1597
1598
1599
1600
1601
1602
1603
1604
1605
1606
1607
1608
1609
1610
1611
1612
1613
1614
1615
1616
1617
1618
1619
1620
1621
1622
1623
1624
1625
1626
1627
1628
1629
1630
1631
1632
1633
1634
1635
1636
1637
1638
1639
1640
1641
1642
1643
1644
1645
1646
1647
1648
1649
1650
1651
1652
1653
1654
1655
1656
1657
1658
1659
1660
1661
1662
1663
1664
1665
1666
1667
1668
1669
1670
1671
1672
1673
1674
1675
1676
1677
1678
1679
1680
1681
1682
1683
1684
1685
1686
1687
1688
1689
1690
1691
1692
1693
1694
1695
1696
1697
1698
1699
1700
1701
1702
1703
1704
1705
1706
1707
1708
1709
1710
1711
1712
1713
1714
1715
1716
1717
1718
1719
1720
1721
1722
1723
1724
1725
1726
1727
1728
1729
1730
1731
1732
1733
1734
1735
1736
1737
1738
1739
1740
1741
1742
1743
1744
1745
1746
1747
1748
1749
1750
1751
1752
1753
1754
1755
1756
1757
1758
1759
1760
1761
1762
1763
1764
1765
1766
1767
1768
1769
1770
1771
1772
1773
1774
1775
1776
1777
1778
1779
1780
1781
1782
1783
1784
1785
1786
1787
1788
1789
1790
1791
1792
1793
1794
1795
1796
1797
1798
1799
1800
1801
1802
1803
1804
1805
1806
1807
1808
1809
1810
1811
1812
1813
1814
1815
1816
1817
1818
1819
1820
1821
1822
1823
1824
1825
1826
1827
1828
1829
1830
1831
1832
1833
1834
1835
1836
1837
1838
1839
1840
1841
1842
1843
1844
1845
1846
1847
1848
1849
1850
1851
1852
1853
1854
1855
1856
1857
1858
1859
1860
1861
1862
1863
1864
1865
1866
1867
1868
1869
1870
1871
1872
1873
1874
1875
1876
1877
1878
1879
1880
1881
1882
1883
1884
1885
1886
1887
1888
1889
1890
1891
1892
1893
1894
1895
1896
1897
1898
1899
1900
1901
1902
1903
1904
1905
1906
1907
1908
1909
1910
1911
1912
1913
1914
1915
1916
1917
1918
1919
1920
1921
1922
1923
1924
1925
1926
1927
1928
1929
1930
1931
1932
1933
1934
1935
1936
1937
1938
1939
1940
1941
1942
1943
1944
1945
1946
1947
1948
1949
1950
1951
1952
1953
1954
1955
1956
1957
1958
1959
1960
1961
1962
1963
1964
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
2026
2027
2028
2029
2030
2031
2032
2033
2034
2035
2036
2037
2038
2039
2040
2041
2042
2043
2044
2045
2046
2047
2048
2049
2050
2051
2052
2053
2054
2055
2056
2057
2058
2059
2060
2061
2062
2063
2064
2065
2066
2067
2068
2069
2070
2071
2072
2073
2074
2075
2076
2077
2078
2079
2080
2081
2082
2083
2084
2085
2086
2087
2088
2089
2090
2091
2092
2093
2094
2095
2096
2097
2098
2099
2100
2101
2102
2103
2104
2105
2106
2107
2108
2109
2110
2111
2112
2113
2114
2115
2116
2117
2118
2119
2120
2121
2122
2123
2124
2125
2126
2127
2128
2129
2130
2131
2132
2133
2134
2135
2136
2137
2138
2139
2140
2141
2142



VII

- wherein R^1 , R^2 , R^3 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B and X are as hereinbefore defined, in the presence of a suitable reducing agent and under appropriate reaction conditions; for example, for formation of compounds of formula I in which D represents -OH, reduction may be performed under mild reaction conditions in the presence of e.g. sodium borohydride and an appropriate organic solvent (e.g. THF); and for formation of compounds of formula I in which D represents H, reduction may be performed by activating the relevant C=O group using an appropriate agent (such as tosylhydrazine) in the presence of a suitable reducing agent (e.g. sodium borohydride or sodium cyanoborohydride) and an appropriate organic solvent (e.g. a lower alkyl alcohol);
- (e) for compounds of formula I in which R^2 and R^3 both represent H, reduction of a corresponding compound of formula VIII,



- wherein R^1 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B, D and X are as hereinbefore defined, and in which the bridgehead C=O group may be activated using an appropriate agent, such as tosylhydrazine, in the presence of a suitable reducing agent (e.g. sodium borohydride or sodium cyanoborohydride) and an appropriate organic solvent (e.g. a lower alkyl alcohol); when the C=O group is activated, the activation step may be carried out at between room and reflux temperature in the presence of an appropriate organic solvent (e.g. a lower alkyl alcohol such as methanol, ethanol or IPA), whereafter the reducing agent may be added to the reaction mixture and the reduction carried out at between 60°C and reflux, advantageously in the presence of a suitable organic acid (e.g. acetic acid);
- (f) for compounds of formula I in which one of R^2 and R^3 represents H and the other represents -OH, reduction of a corresponding compound of formula VIII, as hereinbefore defined, in the presence of a mild reducing agent, e.g. sodium borohydride, and an appropriate organic solvent (e.g. a lower alcohol such as methanol or ethanol);

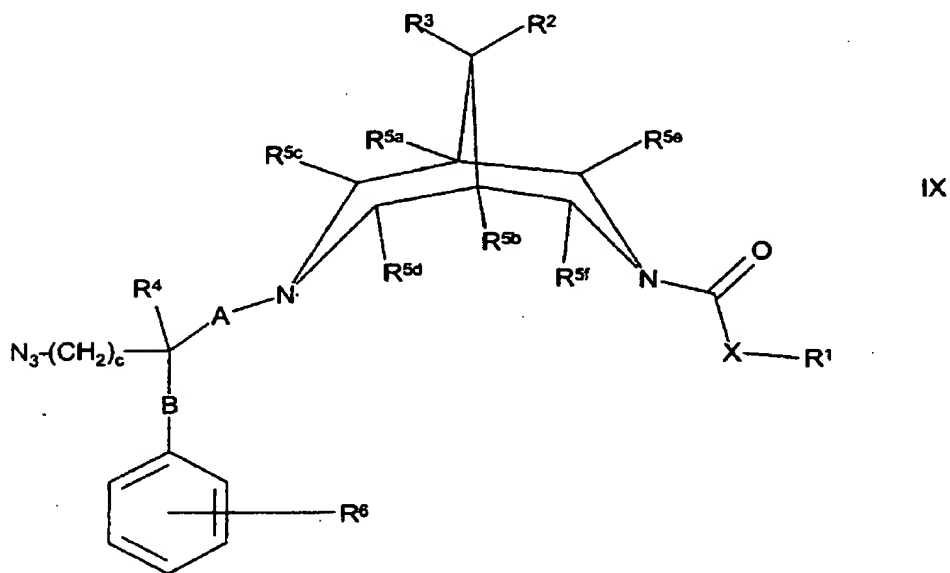
(g) for compounds of formula I in which R^2 and/or R^3 represent $OC(O)R^8$ and R^8 is as hereinbefore defined, coupling of a corresponding compound of formula I in which R^2 and/or R^3 (as appropriate) represent OH and a compound of formula VIIIA,



VIIIA

wherein R^8 is as hereinbefore defined, for example at ambient temperature (e.g. $25^\circ C$) in the presence of a suitable coupling agent (e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), an appropriate catalyst (e.g. 4-dimethylaminopyridine) and a reaction-inert organic solvent (e.g. THF);

(h) for compounds of formula I in which D represents $-(CH_2)_cNH_2$, reduction of a corresponding compound of formula IX,



15

wherein c , R^1 , R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B and X are as hereinbefore defined, for example by hydrogenation at a suitable pressure in the presence of a suitable catalyst (e.g. palladium on carbon) and an appropriate solvent (e.g. a water-ethanol mixture);

- (i) for compounds of formula I in which D represents $-N(R^{11})C(O)NH(R^{17})$, in which R^{11} and R^{17} are as hereinbefore defined, except that R^{11} does not represent $C(O)R^{20}$, reaction of a corresponding compound of formula I in which D represents $-N(R^{11})H$, in which R^{11} is as hereinbefore defined except that it does not represent $C(O)R^{20}$ in which R^{20} is as hereinbefore defined, with a compound of formula X,



- wherein R^{17} is as hereinbefore defined, for example at ambient temperature (e.g. 25°C) in the presence of a suitable solvent (e.g. benzene);

- (j) for compounds of formula I in which D represents $-N(H)[C(O)]_2NH_2$, reaction of a corresponding compound of formula I in which D represents $-NH_2$ with oxalic acid diamide, for example at between -10 and 25°C in the presence of a suitable coupling agent (e.g. 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide), an appropriate activating agent (e.g. 1-hydroxybenzotriazole), a suitable base (e.g. triethylamine) and a reaction-inert organic solvent (e.g. DMF);

- (k) for compounds of formula I in which D represents $-N(R^{11})C(O)R^{18}$, in which R^{11} and R^{18} are as hereinbefore defined, except that R^{11} does not represent $C(O)R^{20}$, reaction of a corresponding compound of formula I in which D represents $-N(R^{11})H$, in which R^{11} is as hereinbefore defined except that it does not represent $C(O)R^{20}$, with a compound of formula XI,



- wherein R^x represents a suitable leaving group, such as C_{1-4} alkoxy, Hal (e.g. Cl, Br) or *p*-nitrophenyl and R^{18} is as hereinbefore defined, for example at between ambient and reflux temperature in the presence of a

suitable solvent (e.g. methanol or DMSO) and (as appropriate) a suitable base (e.g. K_2CO_3 or TEA);

- (l) for compounds of formula I in which D represents $-N(H)R^{10}$ and R^{10} is as
 5 hereinbefore defined except that it does not represent H or $-C(NH)NH_2$,
 reaction of a corresponding compound wherein D represents $-NH_2$ with a
 compound of formula XIA,



- wherein R^{10a} represents R^{10} as hereinbefore defined, except that it does not
 10 represent H or $-C(NH)NH_2$ and L^1 is as hereinbefore defined, for example
 under conditions that are known to those skilled in the art;

- (m) for compounds of formula I which are bispidine-nitrogen N-oxide
 derivatives, oxidation of the corresponding bispidine nitrogen of a
 15 corresponding compound of formula I, in the presence of a suitable
 oxidising agent (e.g. *m*-chloroperbenzoic acid), for example at $0^\circ C$ in the
 presence of a suitable organic solvent (e.g. DCM);

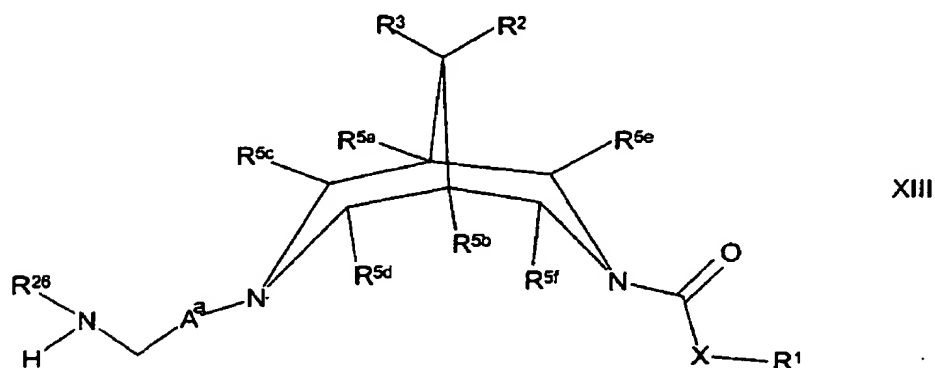
- (n) for compounds of formula I which are C_{1-4} alkyl quaternary ammonium
 20 salt derivatives, in which the alkyl group is attached to a bispidine
 nitrogen, reaction, at the bispidine nitrogen, of a corresponding compound
 of formula I with a compound of formula XII,



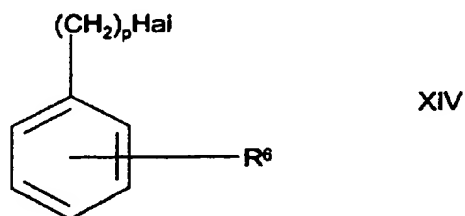
- wherein R^a represents C_{1-4} alkyl and Hal is as hereinbefore defined, for
 25 example at room temperature in the presence of an appropriate organic
 solvent (e.g. DMF), followed by purification (using e.g. HPLC) in the
 presence of a suitable counter-ion provider (e.g. NH_4OAc);

19

(o) for compounds of formula I in which D and R⁴ both represent H, A represents C₁₋₆ alkylene, B represents -N(R²⁶)(CH₂)_p- and R²⁶ and p are as hereinbefore defined, reaction of a compound of formula XIII,



wherein A^a represents C₁₋₆ alkylene and R¹, R², R³, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R²⁶ and X are as hereinbefore defined with a compound of formula XIV,



wherein R⁶, p and Hal are as hereinbefore defined, for example at 40°C in the presence of a suitable organic solvent (e.g. acetonitrile);

(p) reaction of a compound of formula II, as hereinbefore defined, with a compound of formula XV,



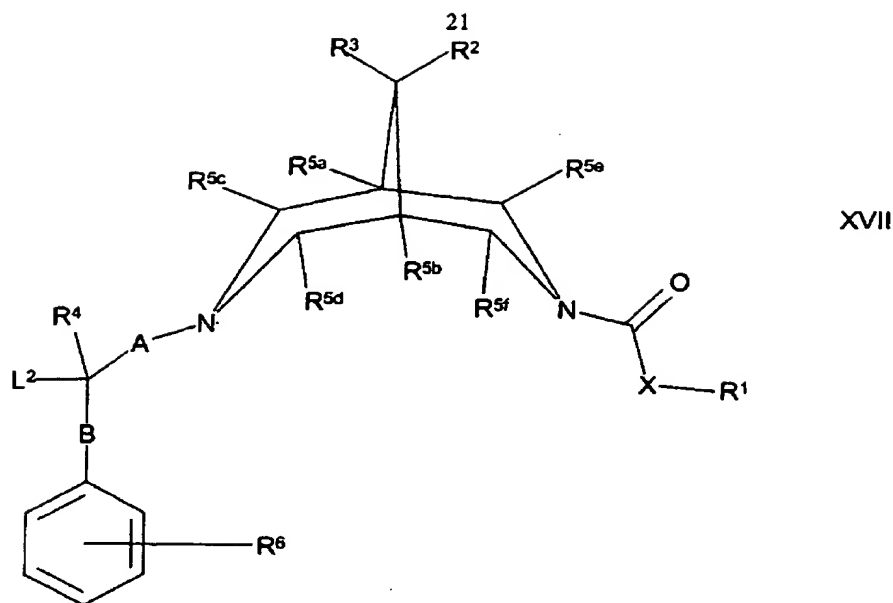
wherein R^1 and X are as hereinbefore defined, in the presence of 1,1'-carbonyldiimidazole, for example by refluxing in the presence of a suitable organic solvent (e.g. THF);

- 5 (q) for compounds of formula I in which R^9 represents optionally substituted C_{1-6} alkyl, optionally substituted $-(CH_2)_d$ -aryl or optionally substituted $-(CH_2)_d$ -Het², reaction of a corresponding compound of formula I, in which D represents OH with a compound of formula XVI,



- 10 wherein R^{9a} represents optionally substituted C_{1-6} alkyl, optionally substituted $-(CH_2)_d$ -aryl or optionally substituted $-(CH_2)_d$ -Het² and d and Het² are as hereinbefore defined, for example at between ambient (e.g. 25°C) and reflux temperature, under Mitsunobu-type conditions (i.e. in the presence of e.g. triphenylphosphine, an azodicarboxylate derivative (e.g. 1,1'-(azodicarbonyl)dipiperidine) and a suitable organic solvent (e.g. dichloromethane));
- 15

- (r) for compounds of formula I in which R^9 represents optionally substituted C_{1-6} alkyl, optionally substituted $-(CH_2)_d$ -aryl or optionally substituted
- 20 $-(CH_2)_d$ -Het², reaction of a compound of formula XVII,



wherein L^2 , R^1 , R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , X , A and B are as hereinbefore defined with a compound of formula XVI as hereinbefore defined, for example at between ambient (e.g. 25°C) and reflux temperature, under Williamson-type conditions (i.e. in the presence of an appropriate base (e.g. KOH or NaH) and a suitable organic solvent (e.g. dimethylsulfoxide or DMF));

(s) for compounds of formula I in which R^9 represents $C(O)R^{12}$ and R^{12} is as hereinbefore defined, reaction of a corresponding compound of formula I in which D represents OH with a compound of formula XVIII,



wherein R^{12} is as hereinbefore defined, for example at ambient temperature (e.g. 25°C) in the presence of a suitable coupling agent (e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), an appropriate catalyst (e.g. 4-dimethylaminopyridine) and a reaction-inert organic solvent (e.g. THF);

(t) for compounds of formula I in which one or both of R^2 and R^3 represent $-N(R^{7a})R^{7b}$ in which one or both of R^{7a} and R^{7b} represents C_{1-6}

alkyl, alkylation of a corresponding compound of formula I in which R^2 and/or R^3 represent $-N(R^{7a})R^{7b}$ (as appropriate) in which R^{7a} and/or R^{7b} (as appropriate) represent H, using a compound of formula XVIIIA,

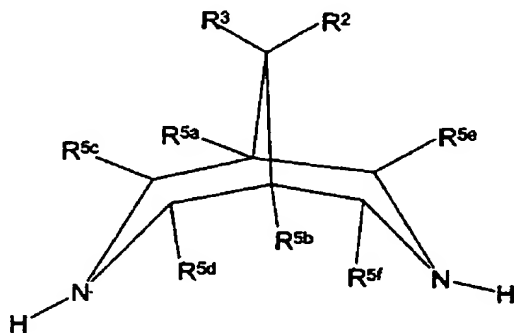


XVIII A

- 5 wherein R^{7c} represents C_{1-6} alkyl and L^1 is as hereinbefore defined, for example under conditions that are well known to those skilled in the art; or

- (u) conversion of one R^6 substituent to another using techniques well known to those skilled in the art.

Compounds of formula II may be prepared by reaction of a compound of formula XIX,

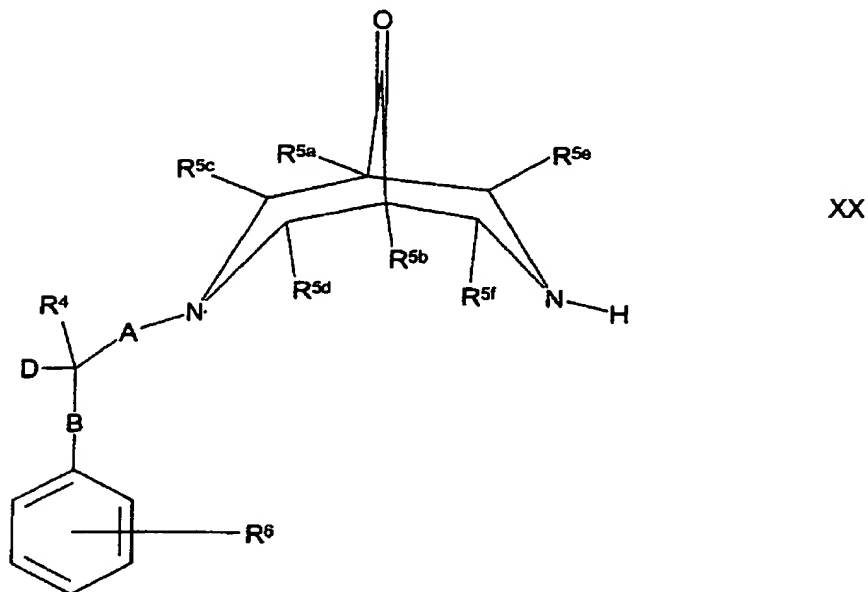


XIX

- 15 wherein R^2 , R^3 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} and R^{5f} are as hereinbefore defined, with a compound of formula VI as hereinbefore defined, for example as described hereinbefore for synthesis of compounds of formula I (process step (c)).

- 20 Compounds of formula II in which A represents CH_2 and D represents OH or $N(H)R^{10}$ may be prepared by reaction of a compound of formula XIX, as hereinbefore defined with a compound of formula V as hereinbefore defined, for example as described hereinbefore for synthesis of compounds of formula I (process step (b)).

Compounds of formula II in which R^2 and R^3 both represent H may be prepared by reduction of a compound of formula XX,



- 5 wherein R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B and D are as hereinbefore defined, and in which the C=O group may be activated using an appropriate agent, such as tosylhydrazine, for example as described hereinbefore for synthesis of compounds of formula I (process step (e)).
- 10 Compounds of formula II in which R^2 represents OH and R^3 represents optionally substituted C_{1-4} alkyl, may be prepared by reaction of a compound of formula XX, or a protected derivative thereof, with a compound of formula XXI,



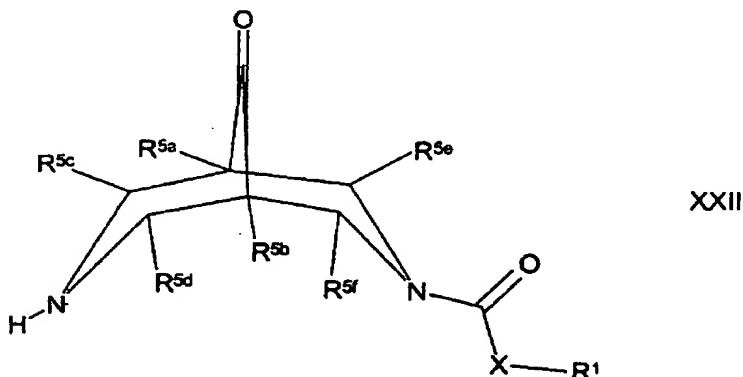
- 15 wherein R^{3a} represents C_{1-4} alkyl (optionally substituted and/or terminated with one or more cyano groups) and Hal is as hereinbefore defined, for example at between -25°C and ambient temperature in the presence of a suitable solvent (e.g. diethyl ether).

Compounds of formula IV may be prepared by reaction of a compound of formula XIX, as hereinbefore defined, with a compound of formula III as hereinbefore defined, for example as described hereinbefore for synthesis of compounds of formula I (process step (a)).

Compounds of formula IV may alternatively be prepared by reaction of a compound of formula XIX, as hereinbefore defined, with a compound of formula XV, as hereinbefore defined, in the presence of 1,1'-carbonyldiimidazole, for example as described hereinbefore for synthesis of compounds of formula I (process step (p)).

Compounds of formula IV in which R^2 and R^3 represent H may alternatively be prepared by reduction of a corresponding compound of formula XXII,

15



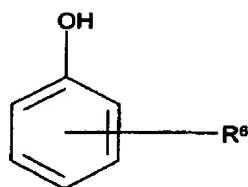
wherein R^1 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} and X are as hereinbefore defined, and in which the bridgehead C=O group may be activated using an appropriate agent, such as tosylhydrazine, for example as described hereinbefore for compounds of formula I (process step (e)).

20

Compounds of formula IV in which one or more of R^{5c} , R^{5d} , R^{5e} and/or R^{5f} represent C_{1-3} alkyl may be prepared by reaction of a compound of formula IV in which R^{5c} , R^{5d} , R^{5e} and/or R^{5f} (as appropriate) represent H, with an appropriate alkylating agent (e.g. dimethyl sulfate), for example in the presence of a suitable strong base (e.g. *n*-BuLi), N,N,N',N'-tetramethylethylenediamine and a reaction-inert solvent (e.g. THF).

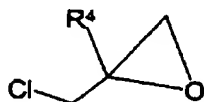
Compounds of formula V may be prepared in accordance with techniques which are well known to those skilled in the art. For example, compounds of formula V in which:

(1) B represents $-CH_2O-$ and Y represents O may be prepared by reaction of a compound of formula XXIII,



XXIII

wherein R^6 is as hereinbefore defined, with a compound of formula XXIV,

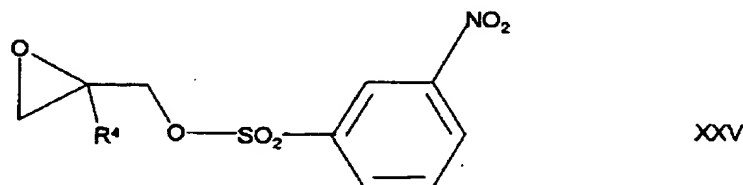


XXIV

wherein R^4 is as hereinbefore defined, for example at elevated temperature (e.g. between 60°C and reflux temperature) in the presence of a suitable base (e.g. K_2CO_3 or NaOH) and an appropriate organic solvent (e.g. acetonitrile or toluene/water), or as otherwise described in the prior art;

(2) B represents $-\text{CH}_2\text{O}-$ and Y represents O may alternatively be prepared by reaction of a compound of formula XXIII, as hereinbefore defined, with a compound of formula XXV,

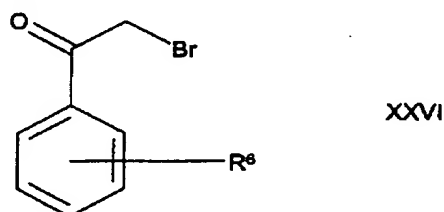
5



wherein R^4 is as hereinbefore defined, for example at between room temperature and elevated temperature (e.g. 40°C) in the presence of a suitable base (e.g. K_2CO_3 or potassium ethoxide) and an appropriate organic solvent (e.g. acetonitrile or DMF);

10

(3) B represents a single bond, Y represents O and R^4 represents H may be prepared by reduction of a compound of formula XXVI,



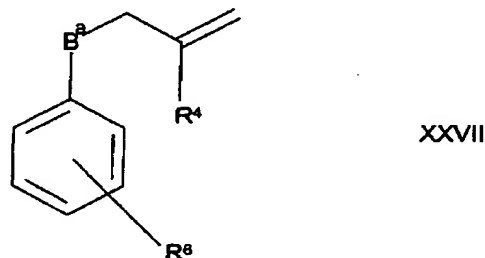
15

wherein R^6 is as hereinbefore defined, for example at between -15°C and room temperature in the presence of a suitable reducing agent (e.g. NaBH_4) and an appropriate organic solvent (e.g. THF), followed by an internal displacement reaction of the resultant intermediate, for example at room temperature in the presence of a suitable base (e.g. K_2CO_3) and an appropriate organic solvent (e.g. acetonitrile);

20

(4) B represents C_{1-4} alkylene, $-(\text{CH}_2)_p\text{N}(\text{R}^{26})-$, $-(\text{CH}_2)_p\text{S}(\text{O})_2-$ or

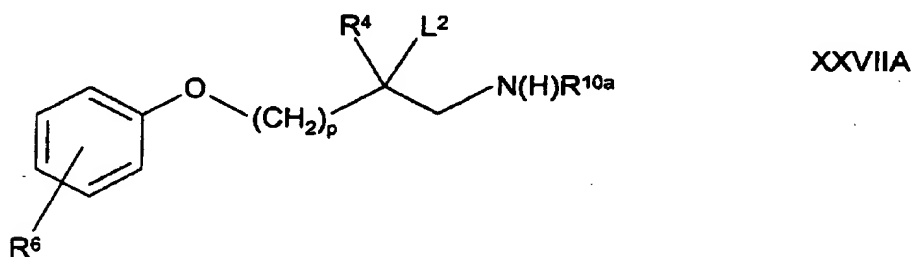
$-(CH_2)_pO-$ (in which latter three groups p represents 1, 2, 3 or 4) and Y represents O may be prepared by oxidation of a compound of formula XXVII,



5 in which B^a represents a single bond, C_{1-3} alkylene, $-(CH_2)_{p-1}N(R^{26})-$, $-(CH_2)_{p-1}S(O)_2-$ or $-(CH_2)_{p-1}O-$ (in which latter three groups p represents 1, 2, 3 or 4) and R^{26} is as hereinbefore defined, in the presence of a suitable oxidising agent (e.g. *m*-chloroperbenzoic acid), for example by refluxing in the presence of a suitable organic solvent (e.g. dichloromethane); or

10

(5) B represents $-(CH_2)_pO-$, Y represents $N(R^{10})$ and R^{10} represents $-S(O)_2R^{15a}$ or $-C(O)OR^{19}$ may be prepared by cyclisation of a compound of formula XXVIIA,



15

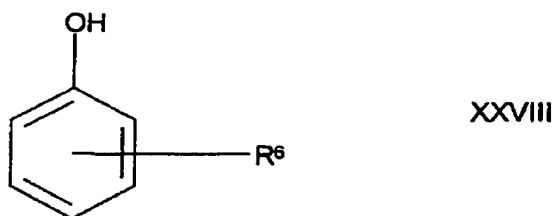
wherein R^{10a} represents $-S(O)_2R^{15a}$ or $-C(O)OR^{19}$ and p , R^4 , R^6 , R^{15a} , R^{19} and L^2 are as hereinbefore defined, for example at between $0^\circ C$ and reflux temperature in the presence of a suitable base (e.g. sodium hydroxide) and

20 an appropriate solvent (e.g. dichloromethane, water, or a mixture thereof)

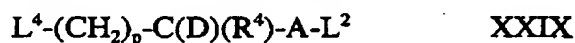
and, if necessary a phase transfer catalyst (such as tetrabutylammonium hydrogensulfate).

Compounds of formula VI may be prepared by standard techniques. For
5 example compounds of formula VI in which:

(1) B represents $-(CH_2)_pO-$ may be prepared by coupling a compound of
formula XXVIII,

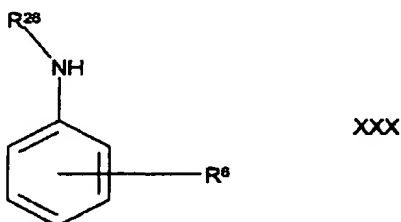


10 wherein R^6 is as hereinbefore defined, to a compound of formula XXIX,



wherein L^4 represents a suitable leaving group (e.g. Hal) and Hal, p, R^4 ,
A, D and L^2 are as hereinbefore defined;

15 (2) B represents $-C(O)N(R^{26})-$ may be prepared by coupling a compound
of formula XXX,



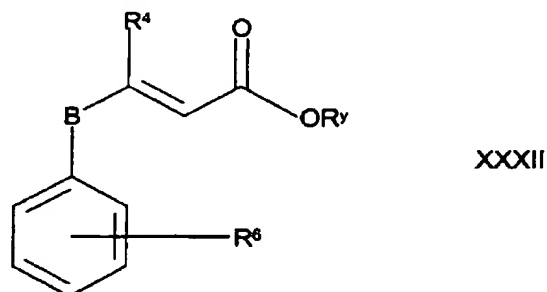
wherein R^6 and R^{26} are as hereinbefore defined, to a compound of formula
XXXI,



20 wherein L^4 , R^4 , A, D and L^2 are as hereinbefore defined;

in both cases, under conditions which are well known to those skilled in the art.

Compounds of formula VI in which A represents C_2 -alkylene and D represents OR^9 , in which R^9 represents optionally substituted C_{1-6} alkyl, optionally substituted $-(CH_2)_d$ -aryl or optionally substituted $-(CH_2)_d$ -Het² may alternatively be prepared by reaction of a compound of formula XVI as hereinbefore defined with a compound of formula XXXII,

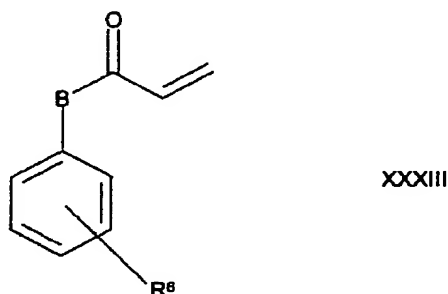


wherein R^y represents C_{1-4} alkyl or aryl (which two groups are optionally substituted with one or more substituents selected from C_{1-4} alkyl or halo) and R^4 , R^6 and B are as hereinbefore defined, for example at between ambient temperature (e.g. $25^\circ C$) and reflux temperature in the presence of a suitable base (e.g. K_2CO_3) and an appropriate organic solvent (e.g. acetonitrile), followed by conversion of the ester functionality to an L^2 group (in which L^2 is as hereinbefore defined), under conditions that are well known to those skilled in the art.

Compounds of formula V and VI in which B represents $-(CH_2)_pS(O)-$ or $-(CH_2)_pS(O)_2-$ may be prepared by oxidation of a corresponding compound of formula V or VI (as appropriate) wherein B represents $-(CH_2)_pS-$, wherein p is as hereinbefore defined, in the presence of an appropriate amount of a suitable oxidising agent (e.g. *m*-chloroperbenzoic acid) and an appropriate organic solvent.

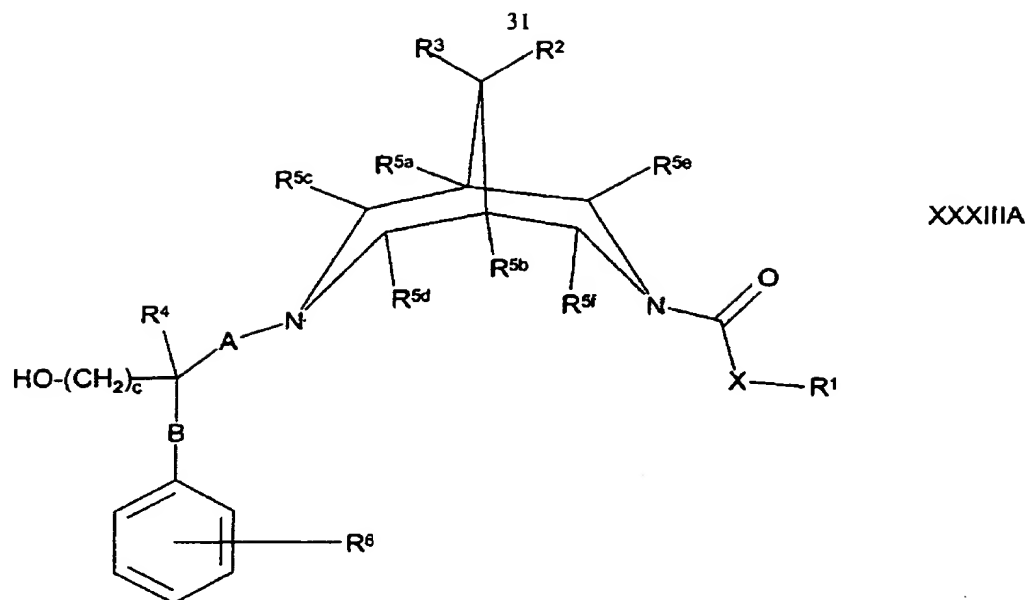
Compounds of formula VII may be prepared in a similar fashion to compounds of formula I (see, for example, process steps (a), (b) or (c)).

- 5 Alternatively, compounds of formula VII in which A represents C_2 alkylene may be prepared by reaction of a corresponding compound of formula IV, as hereinbefore defined with a compound of formula XXXIII,



- 10 wherein R^6 and B are as hereinbefore defined, for example a room temperature in the presence of a suitable organic solvent (e.g. ethanol).

Compounds of formula IX may be prepared by reaction of a corresponding compound of formula XXXIIIA,

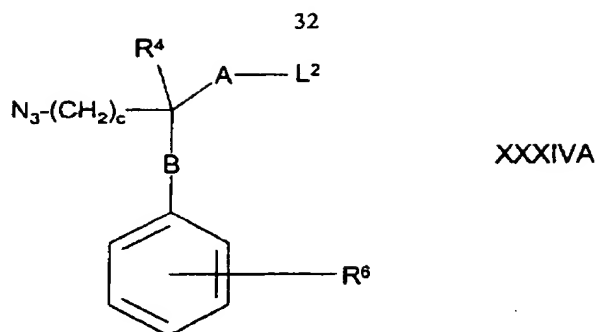


wherein c , R^1 , R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , X , A and B are
 5 as hereinbefore defined with a compound of formula XXXIV,



wherein R^y is as hereinbefore defined, for example at between -10 and 25°C in the presence of a suitable solvent (e.g. dichloromethane), followed by reaction with a suitable source of the azide ion (e.g. sodium azide)
 10 for example at between ambient and reflux temperature in the presence of an appropriate solvent (e.g. DMF) and a suitable base (e.g. NaHCO_3).

Compounds of formula IX may alternatively be prepared by reaction of a
 15 compound of formula IV as hereinbefore defined with a compound of formula XXXIVA,



wherein L^2 , R^4 , R^6 , A, B and c are as hereinbefore defined, for example under analogous conditions to those described hereinbefore for preparation of compounds of formula I (process step (c)).

5

Compounds of formula XIII may be prepared by removing an optionally substituted benzyloxycarbonyl unit from (i.e. deprotecting) a corresponding compound of formula I in which D and R^4 both represent H and B represents $-N(R^{26})C(O)O(CH_2)-$, A represents A^a and A^a is as hereinbefore defined under conditions which are well known to those skilled in the art.

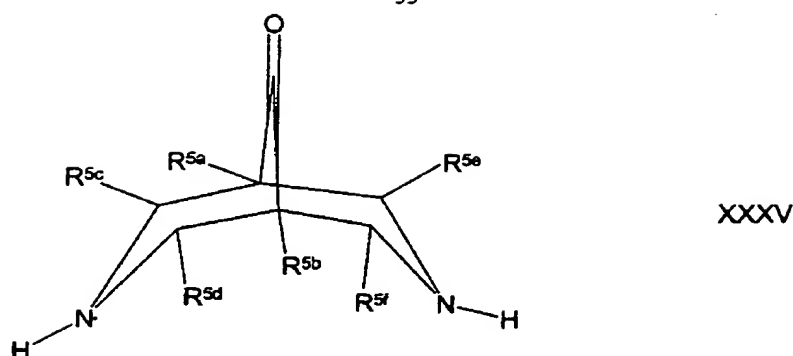
10

Compounds of formula XVII may be prepared by replacement of the OH group of a corresponding compound of formula I in which D represents OH with an L^2 group under conditions that are well known to those skilled in the art.

15

Compounds of formula XIX in which R^2 and R^3 both represent H may be prepared by reduction of a compound of formula XXXV,

20



wherein R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} and R^{5f} are as hereinbefore defined, under appropriate conditions (for example conditions such as those described in respect of the preparation of compounds of formula I (process step (e))).

5

Compounds of formula XIX in which R^2 represents OH and R^3 represents R^{3a} may be prepared by reaction of a corresponding compound of formula XXXV as hereinbefore defined, with a compound of formula XXI as hereinbefore defined, under appropriate conditions (for example conditions such as those described for the production of compounds of formula II in which R^2 represents OH and R^3 represents R^{3a}).

10

Compounds of formula XXXIIIA may be prepared in analogous fashion to corresponding compounds of formula I.

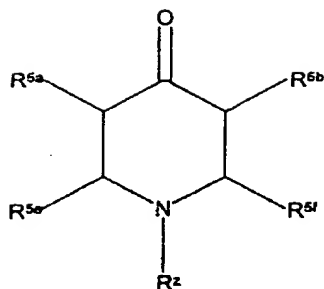
15

Compounds of formula XXXIVA may be prepared in analogous fashion to compounds of formula IX (i.e. from the corresponding alcohol including a $-(CH_2)_cOH$ group).

20

Compounds of formulae VIII, XX, XXII and XXXV (in which, in all cases, R^{5c} and R^{5d} both represent H) may be prepared, advantageously, by reaction of a compound of formula XXXVI,

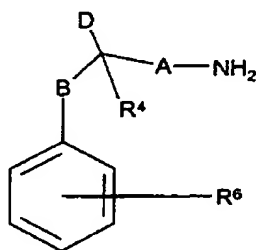
34



XXXVI

wherein R^z represents H or $-C(O)XR^1$ and R^1 , R^{5a} , R^{5b} , R^{5e} , R^{5f} and X are as hereinbefore defined, or a protected derivative thereof, with (as appropriate) either (1) a compound of formula XXXVII,

5



XXXVII

or a protected derivative thereof, wherein R^4 , R^6 , A, B and D are as hereinbefore defined, or (2) NH_3 (or a protected (e.g. benzyl) derivative thereof), in all cases in the presence of a formaldehyde (i.e. an appropriate source of formaldehyde, such as paraformaldehyde or formalin solution).

The formation of compounds of formulae VIII, XX, XXII and XXXV may be carried out in this way for example at between room temperature and reflux (depending upon the concentration of the reactants) in the presence of an appropriate solvent (e.g. ethanol or methanol) and, preferably, in the presence of an organic acid (e.g. a C_{1-6} carboxylic acid, especially acetic acid).

15

The skilled person will also appreciate that this process may also be used to prepare compounds of formula I in which R^{5e} and R^{5f} are H, and R^{5e} and/or R^{5d} are other than H, for example by:

- 5 (i) reacting a compound of formula XXXVI in which R^2 represents $-C(O)XR^1$ and R^{5e} and/or R^{5f} is/are other than H with, for example, benzylamine or a derivative thereof;
- (ii) removal of the $-C(O)XR^1$ unit;
- (iii) reaction at the free bispidine nitrogen of the resultant compound with a compound of formula VI as hereinbefore defined;
- 10 (iv) removal of the benzyl protecting group; and
- (v) reaction at the free bispidine nitrogen of the resultant compound with, for example a compound of formula III or XV as hereinbefore defined,

under conditions well known to those skilled in the art including those
15 described hereinbefore. This reaction will be accompanied by, at some point, conversion of the bridgehead carbonyl functionality to the desired R^2/R^3 groups.

Compounds of formula XXXVII are well known in the literature or are
20 readily available using known techniques. For example, compounds of formula XXXVII wherein D represents $-OH$, R^4 represents H and A represents CH_2 may be prepared by reaction of a compound of formula V in which R^4 represents H with ammonium hydroxide under conditions which are well known to those skilled in the art.

25 Compounds of formulae III, VIIIA, X, XI, XIA, XII, XIV, XV, XVI, XVIII, XVIIIA, XXI, XXIII, XXIV, XXV, XXVI, XXVII, XXVILA, XXVIII, XXIX, XXX, XXXI, XXXII, XXXIII, XXXIV and XXXVI and derivatives thereof, are either commercially available, are known in the

literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

5

Substituents on the aryl (e.g. phenyl), and (if appropriate) heterocyclic, group(s) in compounds defined herein may be converted to other substituents using techniques well known to those skilled in the art. For example, nitrobenzene may be reduced to an aminobenzene, hydroxy may be converted to alkoxy, alkoxy may be hydrolysed to hydroxy etc.

10

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

15

It will be appreciated by those skilled in the art that, in the processes described above, the functional groups of intermediate compounds may be, or may need to be, protected by protecting groups.

20

Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl and alkylcarbonyloxy groups (e.g. methyl- and ethylcarbonyloxy groups). Suitable protecting groups for amino include benzyl, *tert*-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C₁₋₆ alkyl or benzyl esters.

25

The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

Protecting groups may be removed in accordance with techniques which are well known to those skilled in the art and as described hereinafter.

- 5 The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).
- 10 Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned herein may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or
- 15 chemical transformations performed upon, different intermediates to those associated hereinbefore with a particular reaction). This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the type of chemistry
- 20 involved will influence the choice of reagent that is used in the said synthetic steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the synthesis.

- It will also be appreciated by those skilled in the art that, although certain
- 25 protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, they may be administered parenterally or orally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as

"prodrugs". Moreover, certain compounds of formula I may act as prodrugs of other compounds of formula I.

5 All prodrugs of compounds of formula I are included within the scope of the invention.

Some of the intermediates referred to hereinbefore are novel. According to a further aspect of the invention there is thus provided: (a) a compound of formula II as hereinbefore defined, or a protected derivative thereof; (b) a
10 compound of formula IV as hereinbefore defined, or a protected derivative thereof; (c) a compound of formula VIII as hereinbefore defined, or a protected derivative thereof; (d) a compound of formula XX as hereinbefore defined, or a protected derivative thereof; and (e) a compound of formula XXII as hereinbefore defined, or a protected derivative thereof.

15

Medical and pharmaceutical use

The compounds of the invention are useful because they possess pharmacological activity. They are therefore indicated as pharmaceuticals.

20

Thus, according to a further aspect of the invention there is provided the compounds of the invention for use as pharmaceuticals.

25 In particular, the compounds of the invention exhibit myocardial electrophysiological activity, for example as demonstrated in the test described below.

The compounds of the invention are thus expected to be useful in both the prophylaxis and the treatment of arrhythmias, and in particular atrial and ventricular arrhythmias.

5

The compounds of the invention are thus indicated in the treatment or prophylaxis of cardiac diseases, or in indications related to cardiac diseases, in which arrhythmias are believed to play a major role, including ischaemic heart disease, sudden heart attack, myocardial infarction, heart failure,
10 cardiac surgery and thromboembolic events.

In the treatment of arrhythmias, compounds of the invention have been found to selectively delay cardiac repolarization, thus prolonging the QT interval, and, in particular, to exhibit class III activity. Although
15 compounds of the invention have been found to exhibit class III activity in particular, in the treatment of arrhythmias, their mode(s) of activity is/are not necessarily restricted to this class.

According to a further aspect of the invention, there is provided a method of
20 treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound of the invention to a person suffering from, or susceptible to, such a condition.

25

Pharmaceutical preparations

The compounds of the invention will normally be administered orally, subcutaneously, intravenously, intraarterially, transdermally, intranasally, by inhalation, or by any other parenteral route, in the form of pharmaceutical preparations comprising the active ingredient either as a free base, a pharmaceutically acceptable ion exchanger or a non-toxic organic or inorganic acid addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route of administration, the compositions may be administered at varying doses.

The compounds of the invention may also be combined with any other drugs useful in the treatment of arrhythmias and/or other cardiovascular disorders.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Suitable daily doses of the compounds of the invention in therapeutic treatment of humans are about 0.05 to 5.0 mg/kg body weight at parenteral administration.

The compounds of the invention have the advantage that they are effective against cardiac arrhythmias.

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, have a broader range of activity (including exhibiting any combination of class I, class II, class III and/or class IV activity (especially class I, class II and/or class IV activity in addition to class III activity)) than, be more potent than, produce fewer side effects (including a lower incidence of proarrhythmias such as *torsades de pointes*) than, be more easily absorbed than, or that they may have other useful pharmacological properties over, compounds known in the prior art.

Biological Tests

Test A

Primary Electrophysiological Effects In Anaesthetised Guinea Pigs

Guinea pigs weighing between 660 and 1100 g were used. The animals were housed for at least one week before the experiment and had free access to food and tap water during that period.

Anaesthesia was induced by an intraperitoneal injection of pentobarbital (40 to 50 mg/kg) and catheters were introduced into one carotid artery (for blood pressure recording and blood sampling) and into one jugular vein (for drug infusions). Needle electrodes were placed on the limbs for recording of ECGs (lead II). A thermistor was placed in the rectum and the animal was placed on a heating pad, set to a rectal temperature of between 37.5 and 38.5°C.

A tracheotomy was performed and the animal was artificially ventilated with room air by use of a small animal ventilator, set to keep blood gases within

the normal range for the species. In order to reduce autonomic influences both vagi were cut in the neck, and 0.5 mg/kg of propranolol was given intravenously, 15 minutes before the start of the experiment.

- 5 The left ventricular epicardium was exposed by a left-sided thoracotomy, and a custom-designed suction electrode for recording of the monophasic action potential (MAP) was applied to the left ventricular free wall. The electrode was kept in position as long as an acceptable signal could be recorded, otherwise it was moved to a new position. A bipolar electrode
10 for pacing was clipped to the left atrium. Pacing (2 ms duration, twice the diastolic threshold) was performed with a custom-made constant current stimulator. The heart was paced at a frequency just above the normal sinus rate during 1 minute every fifth minute throughout the study.
- 15 The blood pressure, the MAP signal and the lead II ECG were recorded on a Mingograph ink-jet recorder (Siemens-Elema, Sweden). All signals were collected (sampling frequency 1000 Hz) on a PC during the last 10 seconds of each pacing sequence and the last 10 seconds of the following minute of sinus rhythm. The signals were processed using a custom-made program
20 developed for acquisition and analysis of physiological signals measured in experimental animals (see Axenborg and Hirsch, Comput. Methods Programs Biomed. **41**, 55 (1993)).

- 25 The test procedure consisted of taking two basal control recordings, 5 minutes apart, during both pacing and sinus rhythm. After the second control recording, the first dose of the test substance was infused in a volume of 0.2 mL into the jugular vein catheter for 30 seconds. Three minutes later, pacing was started and a new recording was made. Five minutes after the previous dose, the next dose of test substance was

administered. Six to ten consecutive doses were given during each experiment.

Data analysis

5

Of the numerous variables measured in this analysis, three were selected as the most important for comparison and selection of active compounds. The three variables selected were the MAP duration at 75 percent repolarization during pacing, the atrio-ventricular (AV) conduction time (defined as the interval between the atrial pace pulse and the start of the ventricular MAP) during pacing, and the heart rate (defined as the RR interval during sinus rhythm). Systolic and diastolic blood pressure were measured in order to judge the haemodynamic status of the anaesthetised animal. Further, the ECG was checked for arrhythmias and/or morphological changes.

15

The mean of the two control recordings was set to zero and the effects recorded after consecutive doses of test substance were expressed as percentage changes from this value. By plotting these percentage values against the cumulative dose administered before each recording, it was possible to construct dose-response curves. In this way, each experiment generated three dose-response curves, one for MAP duration, one for AV-conduction time and one for the sinus frequency (RR interval). A mean curve of all experiments performed with a test substance was calculated, and potency values were derived from the mean curve. All dose-response curves in these experiments were constructed by linear connection of the data points obtained. The cumulative dose prolonging the MAP duration by 10% from the baseline was used as an index to assess the class III electrophysiological potency of the agent under investigation (D_{10}).

25

The invention is illustrated by way of the following examples.

Examples

5 General Experimental Procedures

Mass spectra were recorded on a Finnigan MAT TSQ 700 triple quadrupole mass spectrometer equipped with an electrospray interface (FAB-MS) and VG Platform II mass spectrometer equipped with an electrospray interface (LC-MS), a Hewlett Packard model 6890 gas chromatograph connected to a
 10 Hewlett-Packard model 5973A mass spectrometer *via* a Hewlett Packard HP-5-MS GC column, or a Shimadzu QP-5000 GC/mass spectrometer (CI, methane). ¹H NMR and ¹³C NMR measurements were performed on a BRUKER ACP 300 and Varian UNITY plus 400 and 500 spectrometers, operating at ¹H frequencies of 300, 400 and 500 MHz respectively, and at
 15 ¹³C frequencies of 75.5, 100.6 and 125.7 MHz respectively. Alternatively, ¹³C NMR measurements were performed on a BRUKER ACE 200 spectrometer at a frequency of 50.3 MHz.

Rotamers may or may not be denoted in spectra depending upon ease of
 20 interpretation of spectra. Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Example 1

25 *tert*-Butyl 7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-2,4-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

(i) 3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane-9-one

The sub-title compound was prepared according to the procedure described in *J. Org. Chem.*, 41 (1976) 1593-1597.

(ii) 3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane

The sub-title compound was prepared according to the procedure described in *J. Org. Chem.*, 41 (1976) 1593-1597, using 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonane-9-one (from step (i) above) in place of N-benzyl-N'-methylbispidone.

(iii) 3-Benzyl-3,7-diazabicyclo[3.3.1]nonane

A solution of 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonane (from step (ii) above; 97 g; 6.4 mmol) in aqueous ethanol (95%) was hydrogenated over 5% Pd/C at 1 atm. until tlc indicated that the reaction was complete. The catalyst was removed by filtration through a pad of Celite®, and the filtrate concentrated under reduced pressure to give the sub-title compound in quantitative yield.

¹³C NMR in CDCl₃: δ 30.1, 33.4, 36.0, 52.5, 59.6, 64.3, 126.9, 128.3, 128.7, 138.8.

(iv) tert-Butyl 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

Di-tert-butyl dicarbonate was added slowly to a solution of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane (from step (iii) above; 60 g; 277 mmol) in THF (600 mL). The reaction was stirred at rt until all of the starting material had been consumed (as indicated by tlc). The solvent was then removed under reduced pressure to give a quantitative yield of the sub-title compound.

(v) tert-Butyl 7-benzyl-2-methyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

N,N,N',N'-Tetramethylethylenediamine (0.98 g; 8.4 mmol) and subsequently *s*-BuLi in cyclohexane (8.46 mL; 1.3 M; 11.0 mmol) was

added to a cooled (-70°C), stirred solution of *tert*-butyl 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (from step (iv) above; 2.65 g; 8.4 mmol) in THF (17 mL) under an inert atmosphere (N₂). The reaction mixture was then allowed to warm to -40°C, at which temperature it was stirred for 1 h. The temperature was lowered again to -70°C, and a solution of dimethyl sulfate (1.64 g; 13.0 mmol) in THF (5 mL) was added. The temperature was then allowed to reach rt before the solvent was evaporated and the residue partitioned between diethyl ether and water. The organic layer was separated, dried (Na₂SO₄), concentrated and subjected to column chromatography (CH₂Cl₂:MeOH; 40:1) to give the sub-title compound in a 30% yield.

(vi) *tert*-Butyl 7-benzyl-2,4-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

The sub-title compound was prepared in a 65% yield according to the procedure described in step (v) above, using *tert*-butyl 7-benzyl-2-methyl-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylate (from step (v) above) in place of *tert*-butyl 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate.

(vii) *tert*-Butyl 2,4-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

The sub-title compound was prepared in quantitative yield according to the procedure described in step (iii) above, using *tert*-butyl 7-benzyl-2,4-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (from step (vi) above) in place of 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonane.

(viii) *tert*-Butyl 7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-2,4-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

The title compound was prepared in 75% yield (after purification by column chromatography) according to the procedure described in Example

2(iii) below, using *tert*-butyl 2,4-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (from step (vi) above) in place of 3-benzyl-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane.

5 FAB-MS: $m/z = 430.0$ ($M + H$)⁺

¹³C NMR in CD₃CN: δ 18.75, 21.04, 28.32, 28.57, 35.38, 36.91, 51.37, 53.24, 55.69, 59.31, 61.03, 62.19, 66.18, 71.85, 79.09, 104.32, 116.23, 119.76, 134.83, 156.62, 163.26

10 Example 2

tert-Butyl 7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

(i) 4-(2-Oxiranylmethoxy)benzonitrile

15 Epichlorohydrin (800 mL) and K₂CO₃ (414 g) were added to a stirred solution of *p*-cyanophenol (238 g) in 2.0 L of acetonitrile. The reaction mixture was brought to reflux under an inert atmosphere for 2 h before being filtered whilst still hot. The resulting filtrate was concentrated to give a clear oil. This was crystallized from di-*iso*-propyl ether to give the
20 sub-title compound in a 75% yield.

(ii) 3-Benzyl-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane

Ethyl acetate (10 mL) saturated with HCl was added to a stirred solution of *tert*-butyl 7-benzyl-2,4-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-
25 carboxylate (from Example 1(vi) above; 1.04 g; 3.01 mmol) in ethyl acetate (5 mL). The reaction mixture was stirred for 2 h at rt, before the solvent was removed under reduced pressure. The residue was redissolved in EtOH and passed through an ion-exchange resin

(Amberlyst® IRA 400), concentrated and then lyophilised to give the sub-title compound in quantitative yield.

5 (iii) 3-Benzyl-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane; Diastereoisomers 1 and 2

A mixture of from 3-benzyl-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane (from step (ii) above; 11.1 g; 45.5 mmol) and 4-(2-oxiranylmethoxy)-benzonitrile (from step (i) above; 7.97 g; 45.5 mmol) in IPA-water (44 mL of 9:1) was stirred at 60°C for 12 h. The reaction mixture was
10 concentrated under reduced pressure and the residue re-dissolved in CH₂Cl₂ and washed with first brine then water. The organic layer was separated, dried (Na₂SO₄) and concentrated. The crude mixture consisted of 4 diastereoisomers (a mixture of 2 diastereomeric pairs). The diastereomeric pairs were separated by chromatography on silica (DCM
15 with 10% NH₃ satd. MeOH).

(iv) 3-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-2,4-dimethyl-3,7-diazabicyclo[3.3.1]nonane; Diastereoisomers 1 and 2

The sub-title compound pairs was prepared in quantitative yield according to the procedure described in Example 1(iii), using the diastereomeric
20 pairs of 3-benzyl-7-[3-(4-cyano-phenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]-nonane (pair from step (iii) above) in place of 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonane.

25 (v) *tert*-Butyl 7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate; Diastereoisomers 1

The title compound was prepared in 50% yield according to the procedure described in Example 1(iv), using 3-[3-(4-cyanophenoxy)-2-hydroxypropyl]-2,4-dimethyl-3,7-diaza-bicyclo[3.3.1]nonane

(Diastereomers 1 from step (iv) above) in place of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane.

FAB-MS: $m/z = 429.9 (M + H)^+$

5 ^{13}C NMR in CDCl_3 : δ 11.13, 19.52, 28.15, 28.49, 34.46, 35.89, 44.80, 48.86, 53.27, 54.98, 61.15, 70.04, 70.72, 79.65, 103.87, 115.33, 119.15, 133.81, 156.23, 162.15

(vi) *tert*-Butyl 7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate; Diastereoisomers 2

10 The title compound was prepared in 50% yield according to the procedure described in Example 1(iv), using 3-[3-(4-cyanophenoxy)-2-hydroxypropyl]-2,4-dimethyl-3,7-diaza-bicyclo[3.3.1]nonane (Diastereoisomers 2 from step (iv) above) in place of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane.

FAB-MS: $m/z = 429.7 (M + H)^+$

^{13}C NMR in CDCl_3 : δ 10.10, 19.68, 27.67, 28.69, 34.73, 36.01, 44.99, 48.92, 51.25, 52.56, 54.72, 65.01, 71.09, 79.49, 103.97, 115.44, 119.24, 133.88, 155.56, 162.26

Example 3

tert-Butyl 7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6-methyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

25

(i) 3-Benzyl-6-methyl-3,7-diazabicyclo[3.3.1]nonane

The sub-title compound was prepared according to the procedure described in Example 2(ii) above, using *tert*-butyl 7-benzyl-2-methyl-3,7-

diazabicyclo[3.3.1]nonane-3-carboxylate (Example 1(v) above) in place of *tert*-butyl 7-benzyl-2,4-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate.

- 5 (ii) 3-Benzyl-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6-methyl-3,7-diazabicyclo[3.3.1]nonane

The sub-title compound was prepared according to the procedure described in Example 2(iii) above, using 3-benzyl-6-methyl-3,7-diazabicyclo[3.3.1]nonane (from step (i) above) in place of 3-benzyl-6,8-
10 dimethyl-3,7-diazabicyclo[3.3.1]nonane.

- (iii) 3-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-2-methyl-3,7-diazabicyclo[3.3.1]nonane

The sub-title compound was prepared according to the procedure described in Example 1(iii) above, using 3-benzyl-7-[3-(4-cyanophenoxy)-
15 2-hydroxypropyl]-6-methyl-3,7-diazabicyclo[3.3.1]nonane (from step (ii) above) in place of 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonane.

- 20 (iv) *tert*-Butyl 7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6-methyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

The title compound was prepared according to the procedure described in Example 1(iv) above, using 3-[3-(4-cyanophenoxy)-2-hydroxypropyl]-2-methyl-3,7-diazabicyclo[3.3.1]nonane (from step (iii) above) in place of
25 3-benzyl-3,7-diazabicyclo[3.3.1]nonane.

FAB-MS: $m/z = 415.8 (M + H)^+$

^{13}C NMR in CDCl_3 : δ 19.45, 28.55, 29.31, 33.77, 36.13, 44.54, 47.65, 57.32, 58.77, 59.84, 60.71, 62.28, 64.98, 70.48, 79.53, 103.96, 115.38, 119.17, 133.86, 155.42, 162.08

Example 4

tert-Butyl 7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

5

(i) 4-[(2*S*)-Oxiranylmethoxy]benzonitrile

The sub-title compound was prepared in a 90% yield according to the procedure described in Example 2(i) above, but using (*R*)-(-)-epichlorohydrin.

10

¹³C NMR in CDCl₃: δ 44.4, 49.7, 69.0, 104.6, 115.3, 119.0, 134.0, 161.6.

(ii) 3-Benzyl-7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane; Diastereoisomers 1 and 2

15 The sub-title compound was prepared according to the procedure described in Example 2(iii) above, using 4-[(2*S*)-oxiranylmethoxy]benzonitrile (from step (i) above) in place of 4-(2-oxiranylmethoxy)benzonitrile, giving a pair of diastereoisomers. the diastereoisomers were separated by column chromatography on silica
20 (DCM and 10% NH₃ satd. MeOH).

(iii) 3-[(2*S*)-3-(4-Cyanophenoxy)-2-hydroxypropyl]-2,4-dimethyl-3,7-diazabicyclo[3.3.1]nonane; Diastereoisomers 1 and 2

25 The sub-title compounds were prepared according to the procedure described in Example 3(iii) above, using 3-benzyl-7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane (diastereoisomers 1 and 2 from step (ii) above) in place of 3-benzyl-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6-methyl-3,7-diazabicyclo[3.3.1]nonane.

(iv) tert-Butyl 7-[(2S)-3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate; Diastereoisomers 1

Prepared according to the procedure described in Example 1(iv) above,
 5 using 3-[(2S)-3-(4-cyanophenoxy)-2-hydroxypropyl]-2-methyl-3,7-diazabicyclo[3.3.1]nonane (distereoisomers 1 from step (iii) above) in place of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane.

ESI-MS: $m/z = 429.9 (M + H)^+$

10 ^{13}C NMR in $CDCl_3$: δ 10.09, 19.66, 27.67, 28.69, 34.72, 36.03, 44.99, 48.91, 51.24, 52.55, 54.71, 65.01, 71.09, 79.48, 103.96, 115.44, 119.23, 133.87, 155.56, 162.26

15 (v) tert-Butyl 7-[(2S)-3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate; Diastereoisomers 2

Prepared according to the procedure described in Example 1(iv) above,
 using 3-[(2S)-3-(4-cyanophenoxy)-2-hydroxypropyl]-2-methyl-3,7-diazabicyclo[3.3.1]nonane (distereoisomers 2 from step (iii) above) in place of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane.

20

ESI-MS: $m/z = 429.8 (M + H)^+$

^{13}C NMR in $CDCl_3$: δ 11.22, 19.59, 27.33, 28.57, 34.54, 35.98, 44.90, 48.94, 53.35, 55.14, 61.29, 70.16, 70.76, 79.75, 103.97, 115.37, 119.23, 133.90, 155.51, 162.20

25

Example 5

The compounds of the above Examples 1 to 4 were tested in Test A above and were all found to exhibit D_{10} values of more than 6.0.

Abbreviations

	AcOH =	acetic acid
	aq. =	aqueous
5	atm. =	atmospheres
	Bu =	butyl
	DMF =	dimethylformamide
	EI =	electron ionisation
	Et =	ethyl
10	EtOAc =	ethyl acetate
	EtOH =	ethanol
	ESI =	electron spray interface
	FAB =	fast atom bombardment
	h =	hours
15	IPA =	<i>iso</i> -propanol
	LC =	liquid chromatography
	HPLC =	high performance liquid chromatography
	Me =	methyl
	MeCN =	acetonitrile
20	MeOH =	methanol
	min. =	minutes
	MS =	mass spectroscopy
	NADPH =	nicotinamide adenine dinucleotide phosphate, reduced form
25	NMR =	nuclear magnetic resonance
	Pd/C =	palladium on carbon
	rt. =	room temperature
	sat. =	saturated
	THF =	tetrahydrofuran

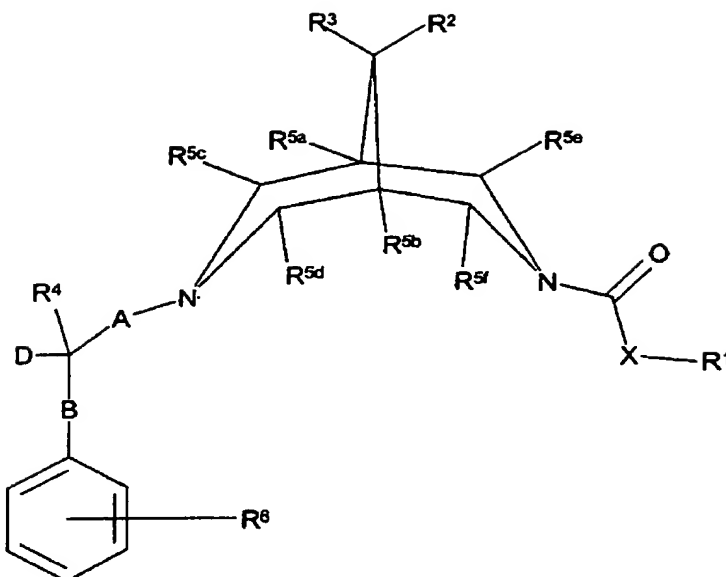
t.l.c. = thin layer chromatography

Prefixes *n*, *s*, *i* and *t* have their usual meanings: normal, iso, secondary and tertiary.

pV99-06-16

Claims

1. A compound of formula I,



5

wherein

R^1 represents C_{1-12} alkyl, $-(CH_2)_a$ -aryl, or $-(CH_2)_a$ -Het¹ (all of which are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy);

10

a represents 0, 1, 2, 3, or 4;

Het¹ represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

15

X represents O or S;

R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} and R^{5f} independently represent H or C_{1-3} alkyl;

R^2 and R^3 independently represent H, C_{1-4} alkyl (optionally substituted and/or terminated with one or more nitro or cyano groups), OR^7 , $N(R^{7a})R^{7b}$, $OC(O)R^8$ or together form $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$;

R^7 and R^8 independently represent H, C_{1-6} alkyl or $-(CH_2)_b$ -aryl (which latter two groups are optionally substituted and/or terminated by one or more substituents selected from $-OH$, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy);

R^{7a} and R^{7b} independently represent H or C_{1-6} alkyl;
b represents 0, 1, 2, 3 or 4;

R^4 represents H or C_{1-6} alkyl;

D represents H, C_{1-4} alkyl, $-OR^9$, or $-(CH_2)_cN(R^{10})(R^{11})$;

R^9 represents H, C_{1-6} alkyl, $-C(O)R^{12}$, $-(CH_2)_d$ -aryl or $-(CH_2)_d$ -Het² (which latter three groups are optionally substituted by one or more substituents selected from $-OH$, halo, cyano, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)R^{13}$, $C(O)OR^{14}$ and/or $-N(H)S(O)_eR^{15}$);

R^{10} represents H, C_{1-6} alkyl, $-(CH_2)_f$ -aryl, $-C(NH)NH_2$, $-S(O)_2R^{15a}$, $-[C(O)]_gN(R^{16})(R^{17})$, $-C(O)R^{18}$ or $-C(O)OR^{19}$;
e represents 0, 1 or 2;

g represent 1 or 2;

R^{11} represents H, C_{1-6} alkyl, $-C(O)R^{20}$ or $-(CH_2)_h$ -aryl (which latter group is optionally substituted and/or terminated (as appropriate) by one or more substituents selected from $-OH$, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

R^{12} , R^{13} , R^{14} , R^{16} , R^{17} , R^{18} , R^{19} and R^{20} independently represent H, C_{1-6} alkyl, Het³ or $-(CH_2)_j$ -aryl (which latter three groups are optionally

substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl and/or C₁₋₆ alkoxy);

R¹⁵ and R^{15a} independently represent C₁₋₆ alkyl, aryl or -(CH₂)_k-aryl (all of which are all optionally substituted and/or terminated (as appropriate) by one or more substituents chosen from halo, nitro, C₁₋₆ alkyl and/or C₁₋₆ alkoxy);

c, d, f, h, j and k independently represent 0, 1, 2, 3 or 4;

Het² and Het³ independently represent five to ten-membered heterocyclic rings containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R⁶ represents one or more optional substituents selected from -OH, cyano, halo, amino, nitro, C₁₋₆ alkyl (optionally terminated by N(H)C(O)OR^{20a}), C₁₋₆ alkoxy, -C(O)N(H)R²¹, -NHC(O)N(H)R²², -N(H)S(O)₂R²³ and/or -OS(O)₂R²⁴;

R²¹ and R²² independently represent H or C₁₋₆ alkyl;

R^{20a}, R²³ and R²⁴ independently represent C₁₋₆ alkyl;

20

A represents a single bond, C₁₋₆ alkylene, -N(R²⁵)(CH₂)_m-, -O(CH₂)_m- or -(CH₂)_mC(H)(OR²⁵)(CH₂)_n- (in which latter three groups, the -(CH₂)_m- group is attached to the bispidine nitrogen atom and which latter four groups are optionally substituted by one or more -OH groups);

25 B represents a single bond, C₁₋₄ alkylene, -(CH₂)_pN(R²⁶)-, -(CH₂)_pS(O)_q-, -(CH₂)_pO- (in which three latter groups, the -(CH₂)_p- group is attached to the carbon atom bearing D and R⁴), -C(O)N(R²⁶)- (in which latter group, the -C(O)- group is attached to the carbon atom bearing D and R⁴),

$-N(R^{26})C(O)O(CH_2)_p-$ or $-N(R^{26})(CH_2)_p-$ (in which latter two groups, the $N(R^{26})$ group is attached to the carbon atom bearing D and R^4);

m, n and p independently represent 0, 1, 2, 3 or 4;

q represents 0, 1 or 2;

5 R^{25} represents H, C_{1-6} alkyl or $C(O)R^{27}$;

R^{26} represents H or C_{1-6} alkyl;

R^{27} represents H, C_{1-6} alkyl, Het^4 or $-(CH_2)_r$ -aryl (which latter two groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

Het^4 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

r represents 0, 1, 2, 3 or 4;

15

or a pharmaceutically acceptable derivative thereof;

provided that:

(a) R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} and R^{5f} do not all simultaneously represent H;

20 (b) R^{5a} and R^{5b} do not represent C_{1-3} alkyl when R^{5c} , R^{5d} , R^{5e} and R^{5f} all represent H; and

(c) when D represents $-OH$ or $-(CH_2)_cN(R^{10})R^{11}$ in which c represents 0, then:-

25 (i) A does not represent $-N(R^{25})(CH_2)_m-$, $-O(CH_2)_m-$ or $-(CH_2)_mC(H)(OR^{25})(CH_2)_n-$ (in which n is 0); and/or

(ii) p does not represent 0 when B represents $-(CH_2)_pN(R^{26})-$, $-(CH_2)_pS(O)_q-$ or $-(CH_2)_pO-$.

2. A compound as claimed in Claim 1, wherein R¹ represents optionally substituted -(CH₂)_a-phenyl, in which a is 0, 1, 2 or 3, or optionally substituted, optionally unsaturated, linear, branched or cyclic, C₁₋₈ alkyl (which latter group may also be interrupted by an oxygen atom).

5

3. A compound as claimed in Claim 1 or Claim 2, wherein R² represents H.

4. A compound as claimed in any one of the preceding claims, wherein R³ represents H.

10

5. A compound as claimed in any one of the preceding claims, wherein R⁴ represents H or C₁₋₃ alkyl.

6. A compound as claimed in any one of the preceding claims, wherein R^{5a} and R^{5b} either both represent H or both represent methyl.

15

7. A compound as claimed in any one of the preceding claims, wherein R^{5c}, R^{5d}, R^{5e} and R^{5f} independently represent H or C₁₋₂ alkyl.

20

8. A compound as claimed in any one of the preceding claims, wherein R⁶ represents one or more substituents selected from C₁₋₆ alkyl (which alkyl group is optionally terminated by a N(H)C(O)OR^{20a} group (in which R^{20a} represents C₁₋₃ alkyl)), cyano, nitro, amino, C(O)N(H)R²¹ and/or -N(H)S(O)₂R²³.

25

9. A compound as claimed in any one of the preceding claims, wherein X represents O.

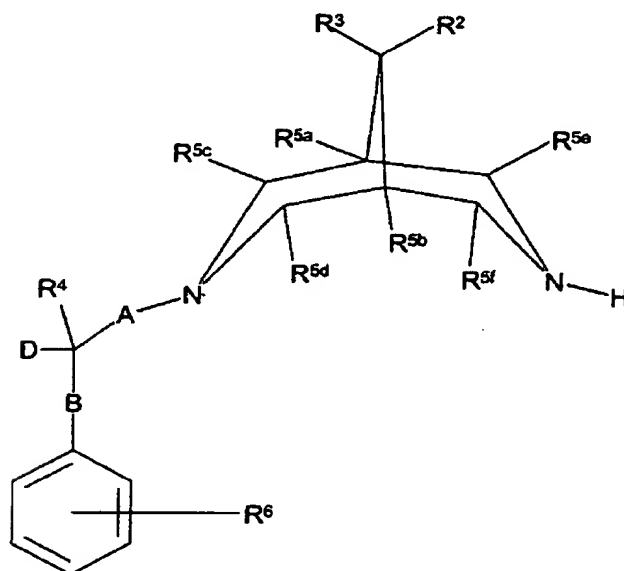
10. A compound as claimed in any one of the preceding claims, wherein A represents a single bond or linear, or branched, C₁₋₄ alkylene (which group is also optionally interrupted by O).
- 5 11. A compound as claimed in any one of the preceding claims, wherein B represents a single bond, C₁₋₄ alkylene, -(CH₂)_pO- or -(CH₂)_pN(R²⁶)- (in which latter two cases p is 1, 2 or 3).
12. A compound as claimed in any one of the preceding claims, wherein D
10 represents H, OR⁹ (in which R⁹ represents H, C₁₋₃ alkyl or optionally substituted phenyl) or N(H)R¹⁰ (in which R¹⁰ represents H or C₁₋₄ alkyl).
13. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 12 in admixture with a pharmaceutically-acceptable
15 adjuvant, diluent or carrier.
14. A pharmaceutical formulation for use in the prophylaxis or the treatment of an arrhythmia, comprising a compound as defined in any one of Claims 1 to 12.
- 20 15. A compound as defined in any one of Claims 1 to 12 for use as a pharmaceutical.
16. A compound as defined in any one of Claims 1 to 12 for use in the
25 prophylaxis or the treatment of an arrhythmia.
17. The use of a compound as defined in any of one Claims 1 to 12 as active ingredient in the manufacture of a medicament for use in the prophylaxis or the treatment of an arrhythmia.

18. The use as claimed in Claim 17, wherein the arrhythmia is an atrial or a ventricular arrhythmia.

19. A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 12 to a person suffering from, or susceptible to, such a condition.

20. A process for the preparation of a compound of formula I as defined in Claim 1 which comprises:

(a) reaction of a compound of formula II,



II

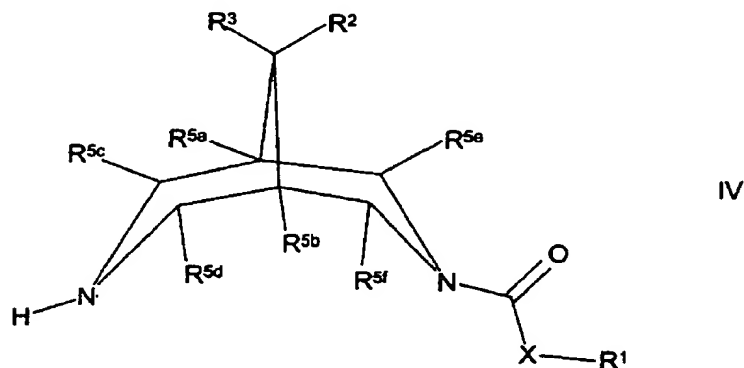
wherein R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B and D are as defined in Claim 1 with a compound of formula III,



III

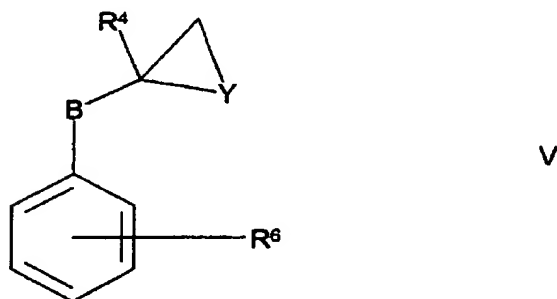
wherein L^1 represents a leaving group and R^1 and X are as defined in Claim 1;

(b) for compounds of formula I in which A represents CH_2 and D represents $-\text{OH}$ or $-\text{N}(\text{H})\text{R}^{10}$, wherein R^{10} is as defined in Claim 1, reaction of a compound of formula IV,



5

wherein R^1 , R^2 , R^3 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} and X are as defined in Claim 1, with a compound of formula V,



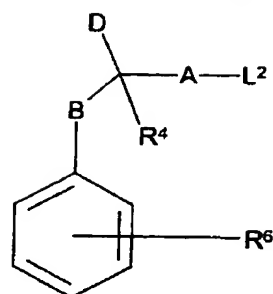
10

wherein Y represents O or $\text{N}(\text{R}^{10})$ and R^4 , R^6 , R^{10} and B are as defined in Claim 1;

(c) reaction of a compound of formula IV, as defined above, with a compound of formula VI,

15

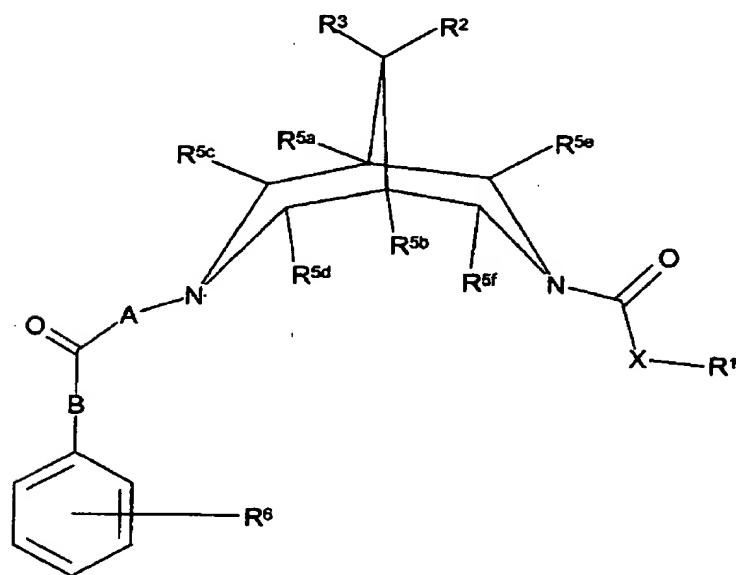
63



VI

wherein L^2 represents a leaving group and R^4 , R^6 , A, B and D are as defined in Claim 1;

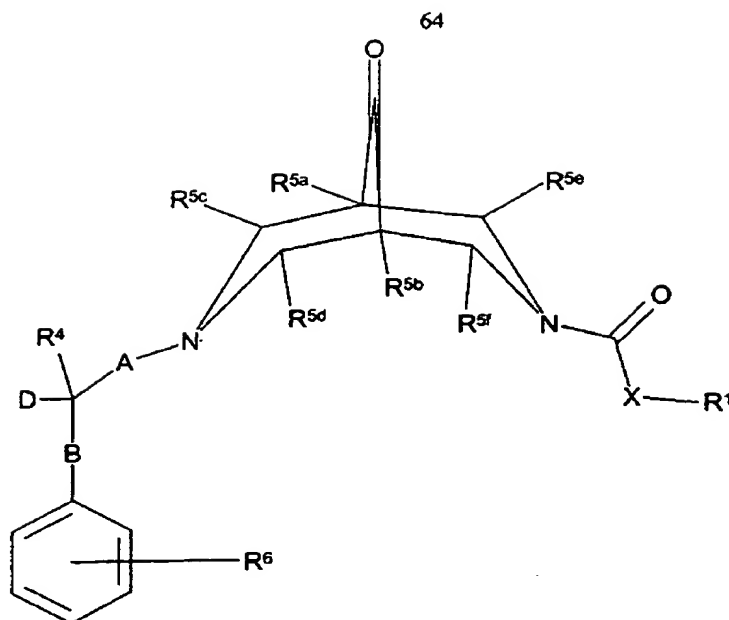
- 5 (d) for compounds of formula I in which D represents H or OH and R^4 represents H, reduction of a compound of formula VII,



VII

- 10 wherein R^1 , R^2 , R^3 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B and X are as defined in Claim 1;

(e) for compounds of formula I in which one of R^2 and R^3 represents H or OH and the other represents H, reduction of a corresponding compound of formula VIII,



VIII

wherein R^1 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B, D and X are as defined in Claim 1;

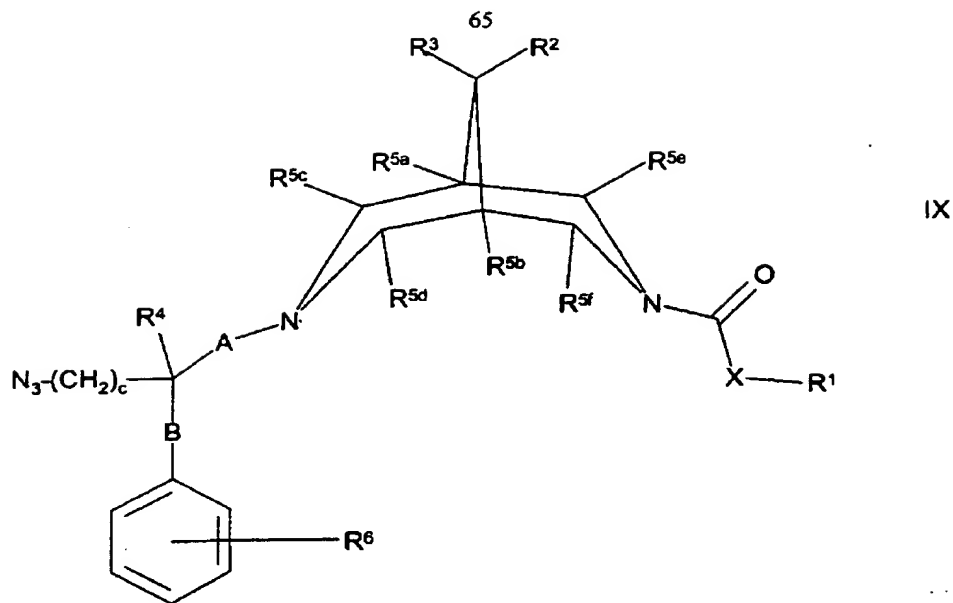
- 5 (f) for compounds of formula I in which R^2 and/or R^3 represent $OC(O)R^8$ and R^8 is as defined in Claim 1, coupling of a corresponding compound of formula I in which R^2 and/or R^3 (as appropriate) represent OH and a compound of formula VIIIA,



VIIIA

- 10 wherein R^8 is as defined in Claim 1;

(g) for compounds of formula I in which D represents $-(CH_2)_cNH_2$, reduction of a corresponding compound of formula IX,



wherein c , R^1 , R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A , B and X are as defined in Claim 1;

- (h) for compounds of formula I in which D represents $-N(R^{11})C(O)NH(R^{17})$,
 5 in which R^{11} and R^{17} are as defined in Claim 1, except that R^{11} does not represent $C(O)R^{20}$, reaction of a corresponding compound of formula I in which D represents $-N(R^{11})H$, in which R^{11} is as defined in Claim 1 except that it does not represent $C(O)R^{20}$ in which R^{20} is as defined in Claim 1, with a compound of formula X,



wherein R^{17} is as defined in Claim 1;

- (i) for compounds of formula I in which D represents $-N(H)[C(O)]_2NH_2$,
 reaction of a corresponding compound of formula I in which D represents $-NH_2$ with oxalic acid diamide;
 15 (j) for compounds of formula I in which D represents $-N(R^{11})C(O)R^{18}$, in which R^{11} and R^{18} are as defined in Claim 1, except that R^{11} does not represent $C(O)R^{20}$, reaction of a corresponding compound of formula I in which D represents $-N(R^{11})H$, in which R^{11} is as defined in Claim 1 except that it does not represent $C(O)R^{20}$, with a compound of formula XI,



XI

wherein R^x represents a suitable leaving group and R^{18} is as defined in Claim 1;

- (k) for compounds of formula I in which D represents $-N(H)R^{10}$ and R^{10} is as defined in Claim 1 except that it does not represent H or $-C(NH)NH_2$,
 5 reaction of a corresponding compound wherein D represents $-NH_2$ with a compound of formula XIA,



XIA

wherein R^{10a} represents R^{10} as defined in Claim 1, except that it does not
 10 represent H or $-C(NH)NH_2$ and L^1 is as defined above;

- (l) for compounds of formula I which are bispidine-nitrogen N-oxide derivatives, oxidation of the corresponding bispidine nitrogen of a corresponding compound of formula I;
- (m) for compounds of formula I which are C_{1-4} alkyl quaternary ammonium
 15 salt derivatives, in which the alkyl group is attached to a bispidine nitrogen, reaction, at the bispidine nitrogen, of a corresponding compound of formula I with a compound of formula XII,

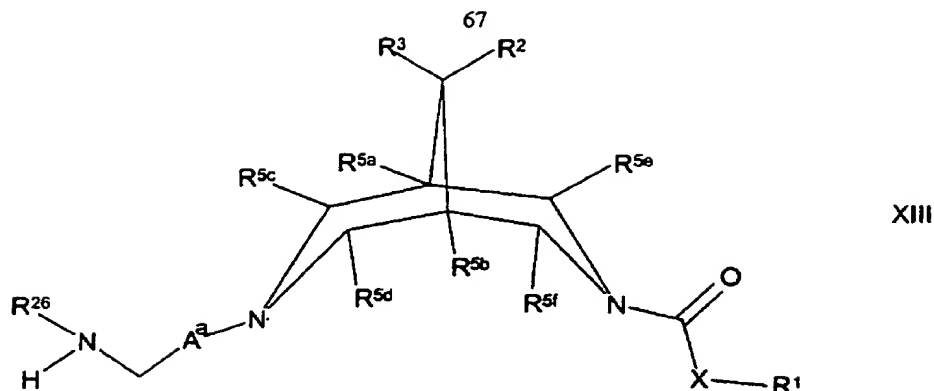


XII

wherein R^a represents C_{1-4} alkyl and Hal represents Cl, Br or I;

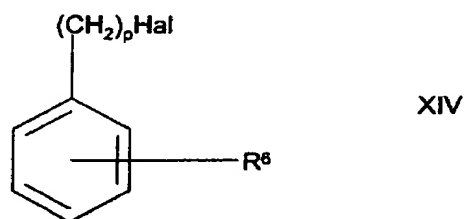
- (n) for compounds of formula I in which D and R^4 both represent H, A represents C_{1-6} alkylene, B represents $-N(R^{26})(CH_2)_p-$ and R^{26} and p are as
 20 defined in Claim 1, reaction of a compound of formula XIII,

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30



wherein A^a represents C₁₋₆ alkylene and R¹, R², R³, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R²⁶ and X are as defined in Claim 1 with a compound of formula XIV,

5



wherein R⁶ and p are as defined in Claim 1 and Hal is defined above;

(o) reaction of a compound of formula II, as defined above, with a compound of formula XV,

10



wherein R¹ and X are as defined in Claim 1, in the presence of 1,1'-carbonyldiimidazole;

(p) for compounds of formula I in which R⁹ represents optionally substituted C₁₋₆ alkyl, optionally substituted -(CH₂)_d-aryl or optionally substituted

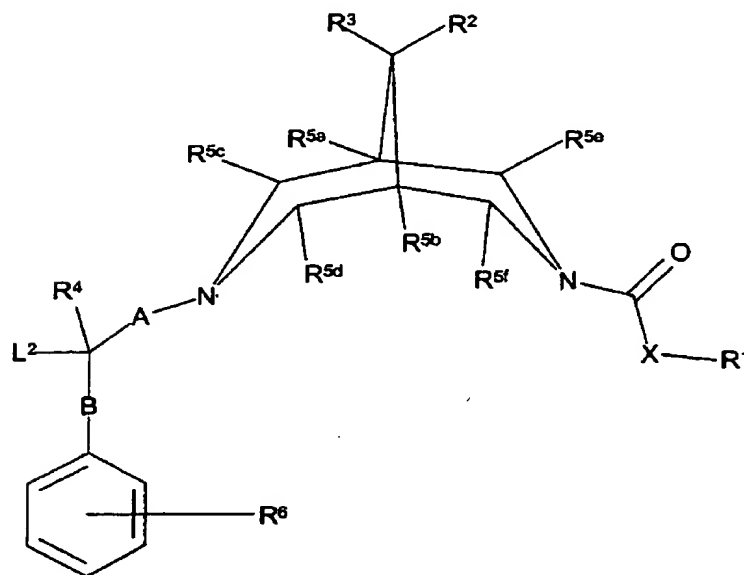
15

-(CH₂)_d-Het², reaction of a corresponding compound of formula I, in which D represents OH with a compound of formula XVI,



wherein R^{9a} represents optionally substituted C_{1-6} alkyl, optionally substituted $-(CH_2)_d$ -aryl or optionally substituted $-(CH_2)_d$ -Het², and d and Het² are as defined in Claim 1;

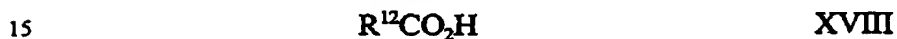
- (q) for compounds of formula I in which R^9 represents optionally substituted C_{1-6} alkyl, optionally substituted $-(CH_2)_d$ -aryl or optionally substituted $-(CH_2)_d$ -Het², reaction of a compound of formula XVII,



XVII

- wherein L^2 is as defined above and R^1 , R^2 , R^3 , R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , X, A and B are as defined in Claim 1 with a compound of formula XVI as defined above;

(r) for compounds of formula I in which R^9 represents $C(O)R^{12}$ and R^{12} is as defined in Claim 1, reaction of a corresponding compound of formula I in which D represents OH with a compound of formula XVIII,



wherein R^{12} is as defined in Claim 1;

- (s) for compounds of formula I in which one or both of R^2 and R^3 represent $-N(R^{7a})R^{7b}$ in which one or both of R^{7a} and R^{7b} represents C_{1-6} alkyl, alkylation of a corresponding compound of formula I in which R^2

69

and/or R^3 represent $-N(R^{7a})R^{7b}$ (as appropriate) in which R^{7a} and/or R^{7b} (as appropriate) represent H, using a compound of formula XVIII,



XVIII

wherein R^{7c} represents C_{1-6} alkyl and L^1 is as defined above;

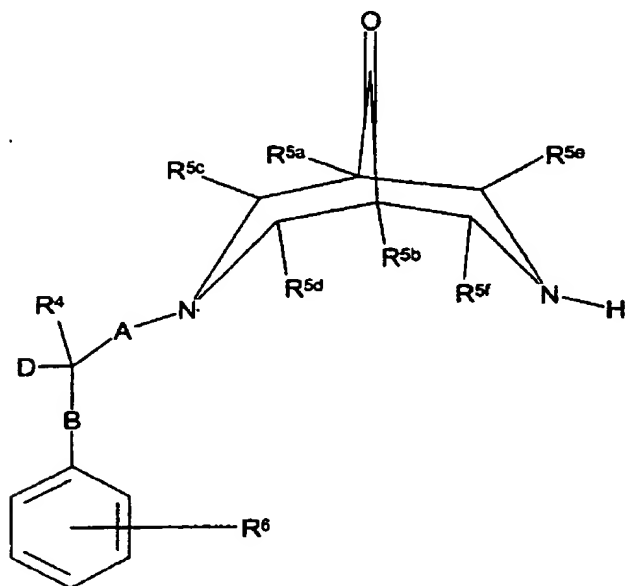
- 5 (t) conversion of one R^6 substituent to another; or
- (u) deprotection of a protected derivative of a compound of formula I as defined in Claim 1.

21. A compound of formula II as defined in Claim 20, or a protected
10 derivative thereof.

22. A compound of formula IV as defined in Claim 20, or a protected derivative thereof.

- 15 23. A compound of formula VIII as defined in Claim 20, or a protected derivative thereof.

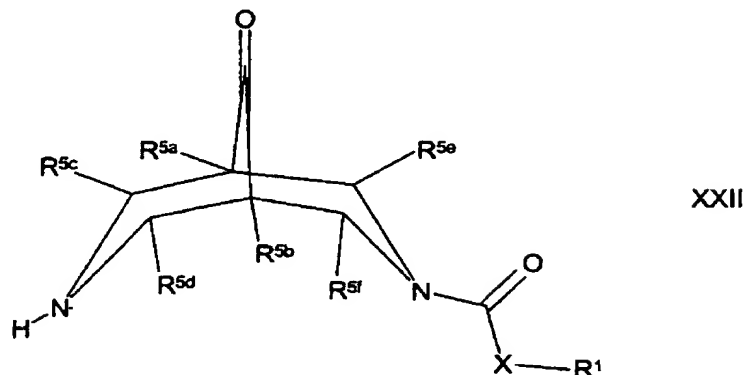
24. A compound of formula XX,



XX

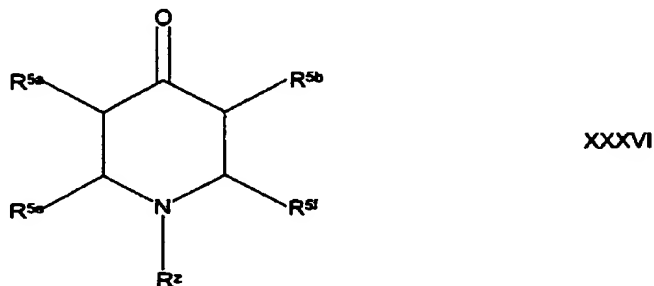
wherein R^4 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} , R^6 , A, B and D are as defined in Claim 1, or a protected derivative thereof.

25. A compound of formula XXII,



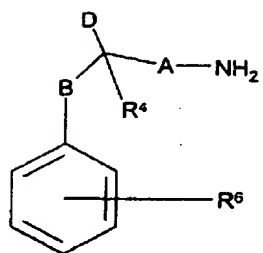
wherein R^1 , R^{5a} , R^{5b} , R^{5c} , R^{5d} , R^{5e} , R^{5f} and X are as defined in Claim 1, or a protected derivative thereof.

26. A process for the preparation of a compound of formula VIII, XX, XXII or XXXV (as defined herein, in which, in all cases, R^{5c} and R^{5d} both represent H), which comprises reaction of a compound of formula XXXVI,



wherein R^2 represents H or $-C(O)XR^1$ and R^1 , R^{5a} , R^{5b} , R^{5c} , R^{5f} and X are as defined in Claim 1, or a protected derivative thereof, with (as appropriate) either:

(1) a compound of formula XXXVII,



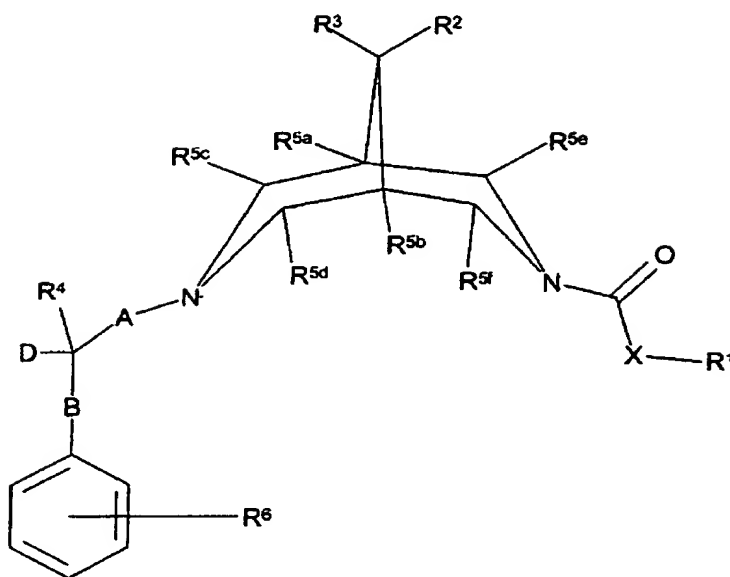
XXXVII

- or a protected derivative thereof, wherein R⁴, R⁶, A, B and D are as defined
- 5 in Claim 1; or
- (2) NH₃ (or a protected derivative thereof),
- in all cases in the presence of a formaldehyde.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100

72
ABSTRACT

There is provided compounds of formula I,



5

wherein R¹, R², R³, R⁴, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{5e}, R^{5f}, R⁶, X, A, B and D have meanings given in the description, which are useful in the prophylaxis and in the treatment of arrhythmias, in particular atrial and ventricular

10 arrhythmias.

This Page Blank (uspto)